3. HEALTH EFFECTS

3.1 INTRODUCTION

The primary purpose of this chapter is to provide public health officials, physicians, toxicologists, and other interested individuals and groups with an overall perspective on the toxicology of chlorine dioxide and chlorite. It contains descriptions and evaluations of toxicological studies and epidemiological investigations and provides conclusions, where possible, on the relevance of toxicity and toxicokinetic data to public health.

A glossary and list of acronyms, abbreviations, and symbols can be found at the end of this profile.

3.2 DISCUSSION OF HEALTH EFFECTS BY ROUTE OF EXPOSURE

To help public health professionals and others address the needs of persons living or working near hazardous waste sites, the information in this section is organized first by route of exposure (inhalation, oral, and dermal) and then by health effect (death, systemic, immunological, neurological, reproductive, developmental, genotoxic, and carcinogenic effects). These data are discussed in terms of three exposure periods: acute (14 days or less), intermediate (15–364 days), and chronic (365 days or more).

Levels of significant exposure for each route and duration are presented in tables and illustrated in figures. The points in the figures showing no-observed-adverse-effect levels (NOAELs) or lowest-observed-adverse-effect levels (LOAELs) reflect the actual doses (levels of exposure) used in the studies. LOAELS have been classified into "less serious" or "serious" effects. "Serious" effects are those that evoke failure in a biological system and can lead to morbidity or mortality (e.g., acute respiratory distress or death). "Less serious" effects are those that are not expected to cause significant dysfunction or death, or those whose significance to the organism is not entirely clear. ATSDR acknowledges that a considerable amount of judgment may be required in establishing whether an end point should be classified as a NOAEL, "less serious" LOAEL, or "serious" LOAEL, and that in some cases, there will be insufficient data to decide whether the effect is indicative of significant dysfunction. However, the Agency has established guidelines and policies that are used to classify these end points. ATSDR believes that there is sufficient merit in this approach to warrant an attempt at distinguishing between "less serious" and "serious" effects. The distinction between "less serious" effects and "serious" effects is

considered to be important because it helps the users of the profiles to identify levels of exposure at which major health effects start to appear. LOAELs or NOAELs should also help in determining whether or not the effects vary with dose and/or duration, and place into perspective the possible significance of these effects to human health.

The significance of the exposure levels shown in the Levels of Significant Exposure (LSE) tables and figures may differ depending on the user's perspective. Public health officials and others concerned with appropriate actions to take at hazardous waste sites may want information on levels of exposure associated with more subtle effects in humans or animals (LOAELs) or exposure levels below which no adverse effects (NOAELs) have been observed. Estimates of levels posing minimal risk to humans (Minimal Risk Levels or MRLs) may be of interest to health professionals and citizens alike.

Estimates of exposure levels posing minimal risk to humans (MRLs) have been made for chlorine dioxide and chlorite. An MRL is defined as an estimate of daily human exposure to a substance that is likely to be without an appreciable risk of adverse effects (noncarcinogenic) over a specified duration of exposure. MRLs are derived when reliable and sufficient data exist to identify the target organ(s) of effect or the most sensitive health effect(s) for a specific duration within a given route of exposure. MRLs are based on noncancerous health effects only and do not consider carcinogenic effects. MRLs can be derived for acute, intermediate, and chronic duration exposures for inhalation and oral routes. Appropriate methodology does not exist to develop MRLs for dermal exposure.

Although methods have been established to derive these levels (Barnes and Dourson 1988; EPA 1990), uncertainties are associated with these techniques. Furthermore, ATSDR acknowledges additional uncertainties inherent in the application of the procedures to derive less than lifetime MRLs. As an example, acute inhalation MRLs may not be protective for health effects that are delayed in development or are acquired following repeated acute insults, such as hypersensitivity reactions, asthma, or chronic bronchitis. As these kinds of health effects data become available and methods to assess levels of significant human exposure improve, these MRLs will be revised.

A User's Guide has been provided at the end of this profile (see Appendix B). This guide should aid in the interpretation of the tables and figures for Levels of Significant Exposure and the MRLs.

3.2.1 Inhalation Exposure

Available human and animal data indicate that airborne chlorine dioxide (ClO_2) primarily acts as a respiratory tract and ocular irritant. Chlorite (ClO_2^-) does not persist in the atmosphere either in ionic form or as chlorite salt. Available information concerning health effects associated with inhalation exposure is limited to chlorine dioxide.

3.2.1.1 Death

Information regarding death in humans exposed to atmospheres of chlorine dioxide is limited to a single case in which a bleach tank worker died after being exposed to an airborne chlorine dioxide concentration of 52 mg/m^3 (18.5 ppm) for an unspecified amount of time (Elkins 1959).

Limited information is available regarding death in laboratory animals exposed to atmospheres of chlorine dioxide. Death resulted from the exposure of a single guinea pig for 44 minutes to an airborne chlorine dioxide concentration of 150 ppm (420 mg/m^3); at the same concentration, exposure for 5 or 15 minutes was not lethal (Haller and Northgraves 1955).

Dalhamn (1957) exposed four rats to approximately 260 ppm (728 mg/m^3) of chlorine dioxide for 2 hours. One of the rats died during exposure and the remaining three rats were sacrificed immediately following the 2-hour exposure period. Microscopic examination revealed pulmonary edema and circulatory engorgement. Dalhamn (1957) also reported death in three of five rats exposed to approximately 10 ppm (28 mg/m^3) of chlorine dioxide, 4 hours/day for up to nine exposures in a 13-day period; clinical signs of toxicity included rhinorrhea and altered respiration.

In another study, rats were repeatedly exposed for 1 month (15 minutes/exposure, 2 or 4 times/day) to atmospheres containing 15 ppm (42 mg/m^3) of chlorine dioxide (Paulet and Desbrousses 1974). Death was noted in 1/10 and 1/15 rats exposed 2 or 4 times/day, respectively. Histological examination of the exposed rats revealed nasal and ocular inflammation, bronchitis, and alveolar lesions. No deaths occurred in rats similarly exposed to 10 ppm (28 mg/m^3) of chlorine dioxide.

3.2.1.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration are recorded in Table 3-1 and plotted in Figure 3-1.

No reports were located in which gastrointestinal, musculoskeletal, endocrine, dermal, or metabolic effects were associated with inhalation exposure of humans or animals to chlorine dioxide or chlorite.

Respiratory Effects. Limited human data indicate that airborne chlorine dioxide is a primary respiratory tract irritant. In a case of accidental inhalation exposure to chlorine dioxide in the paper industry, exposure to 5 ppm (14 mg/m^3) for an unspecified amount of time resulted in signs of respiratory irritation (Elkins 1959). In another case report, a woman experienced coughing, pharyngeal irritation, and headache while mixing a bleach solution that was then used to bleach dried flowers (Exner-Freisfeld et al. 1986). The mixing process resulted in the release of chlorine dioxide. Increasing cough caused the woman to abandon the bleaching process. Seven hours later, the woman began experiencing intensified coughing and dyspnea that resulted in hospitalization (16 hours after the exposure) with clinical findings of cough, dyspnea, tachypnea, and rales. Pulmonary function tests revealed reduced VC (vital capacity) and FEV_1 (forced expiratory volume in 1 second) values and increased resistance. Blood gas analysis and blood chemistry revealed hypoxemia and leukocytosis, respectively. Corticosteroid treatment resulted in the alleviation of clinical signs and improved lung function, which was in the normal range at the 2-year follow-up examination.

Nasal abnormalities (including injection, telangectasia, paleness, cobblestoning, edema, and thick mucus) were observed in 13 individuals (1 man and 12 women) who had been accidently exposed to chlorine dioxide from a leak in a water purification system pipe 5 years earlier (Meggs et al. 1996). These individuals also exhibited sensitivity to respiratory irritants. Nasal biopsies revealed chronic inflammation in the lamina propria of 11/13 chlorine dioxide-exposed individuals, compared with 1/3 control individuals. The severity of inflammation was significantly increased in the chlorine dioxide exposed group, compared to controls.

Several investigators examined the respiratory health of workers who had been occasionally exposed to increased levels of chlorine dioxide resulting from equipment failure (Ferris et al. 1967, 1979; Gloemme and Lundgren 1957; Kennedy et al. 1991). Since the results of these studies are confounded by

Table 3-1 Levels of Significant Exposure to Chlorine Dioxide - Inhalation

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)		LOAEL Serious (ppm)		Reference Chemical Form
ACUTE EXPOSURE									
Death									
1	Rat	2 hr/d for 9 of 13 d					10	100% mortality by day 14	Dalhamn 1957 Chlorine Dioxide
Systemic									
2	Rat	2 hr/d for 9 of 13 d	Resp		10	rhinorrhea and embarrased respiration			Dalhamn 1957 Chlorine Dioxide
3	Rat	3 min/d, 1d/wk, for 3 wk	Resp		760				Dalhamn 1957 Chlorine Dioxide
4	Rat	5 hr/d for 10 wk	Resp	0.1					Dalhamn 1957 Chlorine Dioxide
INTERMEDIATE EXPOSURE									
Systemic									
5	Rat	2 hr/d for 30 d	Resp		10	bronchopneumonia			Paulet and Desbrousses 1970 Chlorine dioxide
			Hemato		10	increased RBC and WBC counts			
			Ocular		10	irritation			
6	Rat	2 hr/d for 30 d	Resp		5	bronchopneumonia			Paulet and Desbrousses 1970 Chlorine dioxide
7	Rat	7 hr/d for 30 d	Resp		2.5	slight respiratory irritation			Paulet and Desbrousses 1970 Chlorine dioxide
8	Rat (Wistar)	5 hr/d 5 d/wk for 2 mo	Resp		1[b]	peribronchiolar edema and vascular congestion in the lungs			Paulet and Desbrousses 1972 Chlorine dioxide

Table 3-1 Levels of Significant Exposure to Chlorine Dioxide - Inhalation (continued)

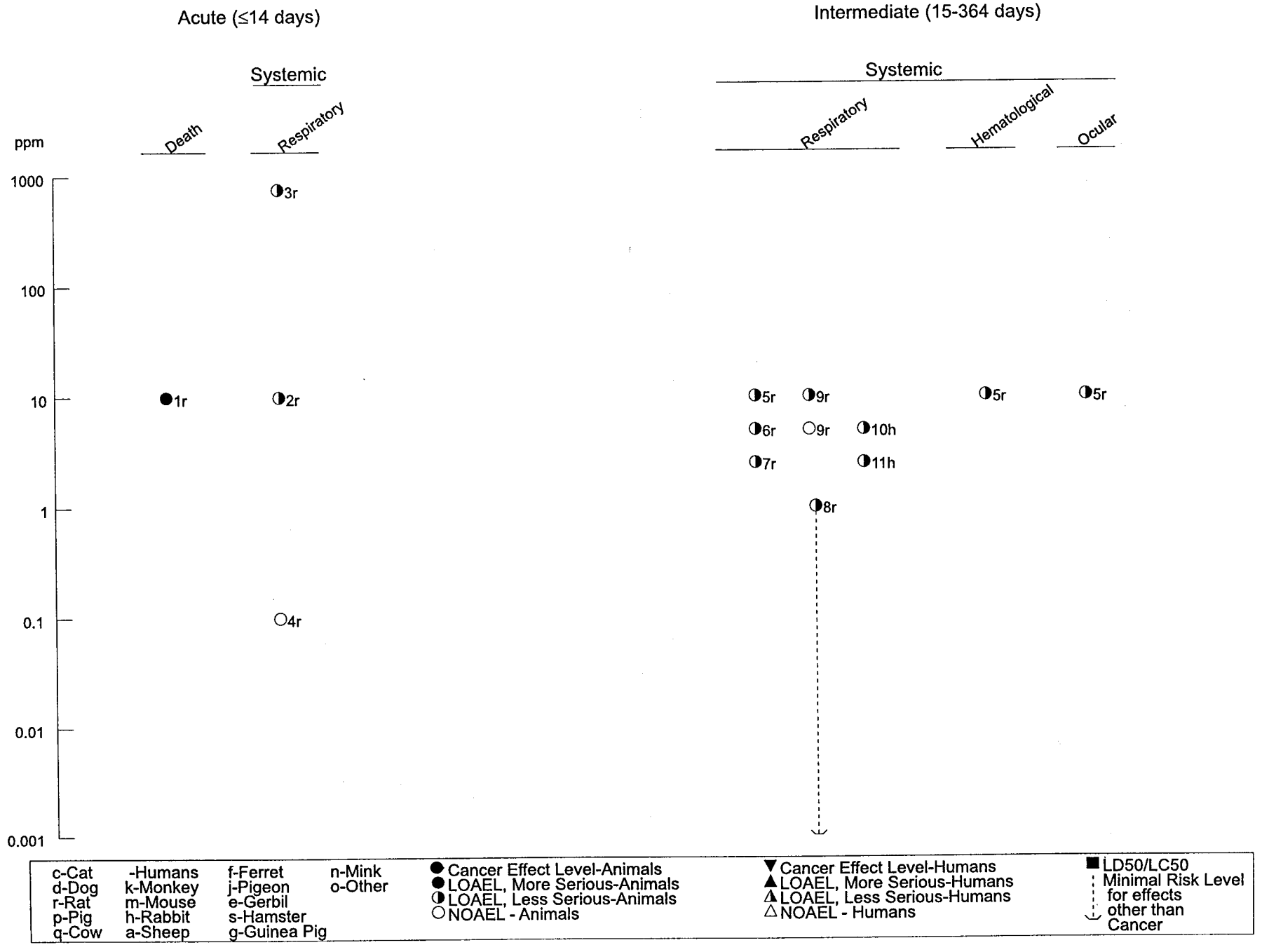
Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (ppm)	LOAEL Less Serious (ppm)	LOAEL Serious (ppm)	Reference Chemical Form
	Systemic						
9	Rat	15 min 2 x/d (or 4 x/d) for 1 mo	Resp	5	10 alveolar irritation		Paulet and Desbrousses 1974 Chlorine dioxide
10	Rabbit	2 hr/d for 30 d	Resp		5 slight bronchopneumonia		Paulet and Desbrousses 1970 Chlorine dioxide
11	Rabbit	4 hr/d for 45 d	Resp		2.5 slight pulmonary irritation		Paulet and Desbrousses 1970 Chlorine dioxide

a The number corresponds to entries in Figure 3-1.

b An intermediate-duration inhalation MRL of 0.001 ppm was derived from a LOAEL of 1 ppm and adjusted to 0.15 ppm (LOAELADJ) to compensate for intermittent exposure, converted to the human equivalent concentration (LOAELHEC) of 0.3 ppm, and then divided by an uncertainty factor of 300 (3 for interspecies extrapolation using dosimetric adjustments, 10 for the use of a LOAEL, and 10 to account for sensitive populations).

d = day(s); hemato = hematological; hr = hour(s); LOAEL = lowest-observed-adverse-effect level; mo = month(s); NOAEL = no-observed-adverse-effect level; Resp = respiratory; wk = week(s)

Figure 3-1 Levels of Significant Exposure to Chlorine Dioxide - Inhalation



concurrent exposure to chlorine gas and/or sulfur dioxide, the reported respiratory effects (such as coughing, wheezing, shortness of breath, and excess phlegm) could not be specifically attributed to chlorine dioxide.

Animal studies also indicate that the respiratory system is a major target of toxicity following inhalation exposure to chlorine dioxide. Dalhamn (1957) reported the results of several inhalation studies in laboratory animals. In one study, a single 2-hour inhalation exposure of four rats to a chlorine dioxide concentration of 260 ppm (728 mg/m^3) resulted in pulmonary edema and nasal bleeding. Respiratory distress was reported in three other rats subjected to 3 weekly 3-minute exposures to decreasing concentrations of airborne chlorine dioxide from 3,400 to 800 ppm (from 9,520 to 2,240 mg/m^3); bronchopneumonia was observed in two of these rats. In a third rat study, repeated exposure to approximately 10 ppm (28 mg/m^3) of chlorine dioxide (4 hours/day for 9 days in a 13-day period) resulted in rhinorrhea, altered respiration, and respiratory infection. No indications of adverse effects were seen in rats exposed to approximately 0.1 ppm (0.28 mg/m^3) of chlorine dioxide 5 hours /day for 10 weeks.

Paulet and Desbrousses (1970, 1972, 1974) conducted a series of studies in which laboratory animals were exposed to atmospheres of chlorine dioxide. Nasal discharge and localized bronchopneumonia (with desquamation of alveolar epithelium) were noted in rats exposed to an airborne concentration of 10 ppm (28 mg/m^3), 2 hours/day for 30 days. Another group of rats exposed to a concentration of 5 ppm (14 mg/m^3) exhibited similar, but less severe, respiratory tract effects. Bronchial inflammation and alveolar congestion and hemorrhage were observed in rats exposed to 2.5 ppm (7 mg/m^3), 7 hours/day for 30 days. Alveolar congestion and hemorrhage were also seen in rabbits following inhalation exposure to 2.5 ppm (7 mg/m^3), 4 hours/day for 45 days. In a group of rats and rabbits sacrificed 15 days after exposure termination, recovery from the pulmonary lesions was apparent (Paulet and Desbrousses 1970). Vascular congestion and peribronchiolar edema were noted in the lungs of rats exposed to a concentration of 1 ppm (2.8 mg/m^3), 5 hours/day, 5 days/week for 2 months (Paulet and Desbrousses 1972). The LOAEL of 1 ppm for respiratory effects, identified in this study, served as the basis for the derivation of an intermediate-duration inhalation MRL for chlorine dioxide. In another rat study, exposure to concentrations of 10 or 15 ppm (28 or 42 mg/m^3) for periods as short as 15 minutes (2 or 4 times/day for 1 month) resulted in nasal, bronchial, and alveolar inflammation. These effects had subsided in a 15 ppm (42 mg/m^3) group of rats sacrificed 15 days following exposure termination. This study identified a NOAEL of 5 ppm (14 mg/m^3) for respiratory effects (Paulet and Desbrousses 1974).

Cardiovascular Effects. Information regarding cardiovascular effects in humans following inhalation exposure to chlorine dioxide is limited to a single account of tachycardia that developed in a woman several hours after having been exposed to an unknown concentration of chlorine dioxide that had triggered respiratory effects severe enough to force her to leave the area where she had been bleaching dried flowers (Elkins 1959). The tachycardia was likely secondary to the primary respiratory effects.

Circulatory engorgement was observed in rats that had been exposed to atmospheres containing a chlorine dioxide concentration of approximately 260 ppm (728 mg/m^3) for 2 hours (Dalhamn 1957). This effect was likely secondary to respiratory distress.

Hematological Effects. Information regarding hematological effects in humans following inhalation exposure to chlorine dioxide is limited to a single account of marked leukocytosis diagnosed in a woman several hours after she had been exposed to an unknown concentration of chlorine dioxide that triggered respiratory effects severe enough to force her to leave the area where she had been bleaching dried flowers (Elkins 1959).

Significantly increased blood erythrocyte and leukocyte levels were reported in rats exposed to atmospheres containing a chlorine dioxide level of approximately 10 ppm (28 mg/m^3), 2 hours/day for 30 days (Paulet and Desbrousses 1970). These effects were not seen in a group of rats similarly exposed to 5 ppm (14 mg/m^3).

Hepatic Effects. No information was located regarding hepatic effects in humans following inhalation exposure to chlorine dioxide.

Paulet and Desbrousses (1974) found no signs of liver effects in rats exposed to atmospheres containing chlorine dioxide levels as high as 10 ppm (28 mg/m^3), 2 hours/day for 30 days. On the other hand, Dalhamn (1957) reported acute liver congestion in rats that had been exposed for 4 hours/day over 9 days in a 13-day period. However, the liver congestion may have been secondary to primary respiratory effects.

Renal Effects. No information was located regarding renal effects in humans following inhalation exposure to chlorine dioxide.

Evidence of renal effects in animals is limited to a single report of renal hyperemia in two of three rats subjected to 3 weekly 3-minute exposures to decreasing concentrations of airborne chlorine dioxide from 3,400 to 800 ppm (from 9,520 to 2,240 mg/m^3); however, two of three control rats similarly exhibited renal hyperemia (Dalhamn 1957).

Ocular Effects. Workers employed at a sulfite-cellulose production facility reported ocular discomfort that was associated with periods when equipment failure resulted in relatively high air concentrations of chlorine dioxide (Gloemme and Lundgren 1957). However, this finding was confounded by concurrent exposure to chlorine gas and sulfur dioxide.

Animal studies indicate that exposure to chlorine dioxide at airborne concentrations $10 ppm (28 mg/m^3) may result in ocular irritation (Dalhamn 1957; Paulet and Desbrousses 1970, 1974).

Body Weight Effects. No information was located regarding body weight effects in humans following inhalation exposure to chlorine dioxide.

Limited animal data indicate that repeated inhalation exposure to chlorine dioxide concentrations $10 ppm (28 mg/m^3) may result in depressed body weight gain (Dalhamn 1957; Paulet and Desbrousses 1970); however, this effect may be secondary to primary respiratory effects.

No reports were located in which the following health effects in humans or animals could be associated with inhalation exposure to chlorine dioxide:

3.2.1.3 Immunological and Lymphoreticular Effects

3.2.1.4 Neurological Effects

3.2.1.5 Reproductive Effects

3.2.1.6 Developmental Effects

3.2.1.7 Cancer

3.2.2 Oral Exposure

3.2.2.1 Death

No information was located regarding death in humans following oral exposure to chlorine dioxide or chlorite.

Shi and Xie (1999) indicated that an acute oral LD_{50} value (a dose expected to result in death of 50% of the dosed animals) for stable chlorine dioxide was >10,000 mg/kg in mice. In rats, acute oral LD_{50} values for sodium chlorite ($NaClO_2$) ranged from 105 to 177 mg/kg (equivalent to 79–133 mg chlorite/kg) (Musil et al. 1964; Seta et al. 1991; Sperling 1959).

No exposure-related deaths were observed in rats receiving chlorine dioxide in the drinking water for 90 days at concentrations that resulted in approximate doses as high as 11.5 mg/kg/day in males and 14.9 mg/kg/day in females (Daniel et al. 1990).

In a 14-day range-finding study of rats administered gavage doses of sodium chlorite in the range of 25–200 mg/kg/day (equivalent to 18.6–149.2 mg chlorite/kg/day), one exposure-related death was observed in each sex (Harrington et al. 1995a). The deaths occurred on treatment days 2 and 3. No treatment-related deaths occurred in the groups receiving chlorite doses #56 mg/kg/day. In the 13-week main study performed by these investigators, treatment-related mortality was noted between exposure weeks 10 and 13 in 4/30 rats (3 males and 1 female) receiving sodium chlorite by gavage at a level resulting in a chlorite dose of 80 mg/kg/day. No treatment-related mortality was observed at chlorite dose levels #18.6 mg/kg/day. Death was noted in all four female rats that were administered sodium chlorite by gavage at a dose level of 200 mg/kg/day (equivalent to 150 mg chlorite/kg/day) on gestation days 8–10 (Couri et al. 1982b).

Haag (1949) exposed groups of rats to chlorine dioxide in the drinking water for 2 years at concentrations that resulted in estimated doses of 0.07, 0.13, 0.7, 1.3, or 13 mg/kg/day. Survival was significantly decreased during the second year of exposure at the 13 mg/kg/day dose level, but not in lower dose groups. Survival was not significantly decreased in groups of rats exposed to chlorite (as sodium chlorite) in the drinking water for 2 years at concentrations that resulted in estimated chlorite doses as high as 81 mg/kg/day (Haag 1949). In another chronic study (Kurokawa et al. 1986), survival was not adversely

affected in rats given sodium chlorite in the drinking water at concentrations that resulted in estimated chlorite doses as high as 32.1 mg/kg/day in males and 40.9 mg/kg/day in females. However, this study was terminated after 85 weeks of treatment, due to widespread Sendai viral infection in both treatment groups and controls. Exposure of mice to sodium chlorite for up to 85 weeks at concentrations resulting in estimated chlorite doses as high as 90 mg/kg/day did not appear to adversely affect survival. However, control males exhibited markedly reduced survival after 30 weeks of exposure, which was attributed to severe fighting (Kurokawa et al. 1986).

Selected LD_{50} values for chlorite are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.2 Systemic Effects

The highest NOAEL values and all LOAEL values from each reliable study for each systemic effect in each species and duration are recorded in Table 3-2 and plotted in Figure 3-2.

No reports were located in which cardiovascular, musculoskeletal, dermal, ocular, or metabolic effects were associated with oral exposure of humans or animals to chlorine dioxide or chlorite.

Respiratory Effects. Extremely limited information is available regarding respiratory effects in humans following oral exposure to chlorine dioxide or chlorite. Respiratory distress was diagnosed in a patient who had ingested 10 g of sodium chlorite dissolved in 100 mL of water (Lin and Lim 1993). However, the respiratory distress was likely secondary to other effects such as severe methemoglobinemia. No adverse effects on respiration rate were seen in healthy adult males who ingested chlorine dioxide or chlorite every 3 days at increasing doses of 0.1, 1, 5, 10, 18, and 24 mg/day or 0.01, 0.1, 0.5, 1.0, 1.8, or 2.4 mg/day, respectively (Lubbers et al. 1981). Assuming an average body weight of 70 kg, the individual doses were approximately 0.0014, 0.014, 0.070, 0.140, 0.26, and 0.34 mg/kg/day, respectively, for chlorine dioxide and a factor of 10 lower for respective chlorite doses. No adverse effects on respiration rate were observed in other healthy adult males who ingested chlorine dioxide or chlorite in daily amounts of 2.5 mg (0.04 mg/kg/day) for 12 weeks (Lubbers et al. 1981).

Table 3-2 Levels of Significant Exposure to Chlorine Dioxide And Chlorite - Oral

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	ACUTE EXPOSURE						
	Death						
1	Rat	1x (GW)				140 M LD50	Musil et al. 1964 Chlorite
	INTERMEDIATE EXPOSURE						
	Systemic						
2	Mouse A/J	12 hrs d 30 d (W)	Hemato	25			Moore and Calabrese 1982 Chlorine Dioxide
3	Mouse A/J	12 hrs/d 30 d (W)	Hemato		19 Increased average corpuscular volume and osmotic fragility		Moore and Calabrese 1982 Chlorite
4	Mouse C57L/J	12 hrs/d 30 d (W)	Hemato		19		Moore and Calabrese 1982 Sodium Chlorite
	Reproductive						
5	Rat (Long- Evans)	66-76 d (W)		0.9 M	9 M decreased progressive sperm movement		Carlton et al. 1987 Chlorite
6	Rat (Long- Evans)	1x/d for 9 wk (GW)		10			Carlton et al. 1991 Chlorine dioxide
7	Rat (Sprague-Dawley)	16 wk (W)		29			Gill et al. 2000 Chlorite
8	Rat (Sprague-Dawley)	13 wk (W)		1.3		13 decreased number of implants	Suh et al. 1983 Chlorine dioxide

Table 3-2 Levels of Significant Exposure to Chlorine Dioxide And Chlorite - Oral (continued)

Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Developmental						
9	Rat (Long- Evans)	8 wk (W)		0.9 M	9 M decreased serum T3 and T4 levels		Carlton et al. 1987 Chlorite
10	Rat (Sprague-Dawley)	16 wk (W)		2.9[b] M	5.7 M lowered auditory startle response amplitude on postnatal day 24		Gill et al. 2000 Chlorite
11	Rat (Sprague-Dawley)	9 wk (W)			13 M decreased litter weight and exploratory activity		Mobley et al. 1990 Chlorine dioxide
12	Rat (Sprague-Dawley)	9 wk (W)		2.6 M	5.2 M decreased exploratory activity on postnatal days 36-39		Mobley et al. 1990 Chlorite
13	Rat (Sprague-Dawley)	8 wk (W)		2.6 F	13 F altered serum thyroid hormone levels		Orme et al. 1985 Chlorine dioxide
14	Rat (Sprague-Dawley)	ppd 5-20 (W)			14 decreased activity, decreased serum T4		Orme et al. 1985 Chlorine dioxide
15	Rat (Sprague-Dawley)	13 wk (W)		1.3		13 decreased number of live fetuses	Suh et al. 1983 Chlorine dioxide
16	Rat (Sprague-Dawley)	13 wk (W)		1.3			Suh et al. 1983 Chlorite

Table 3-2 Levels of Significant Exposure to Chlorine Dioxide And Chlorite - Oral (continued)

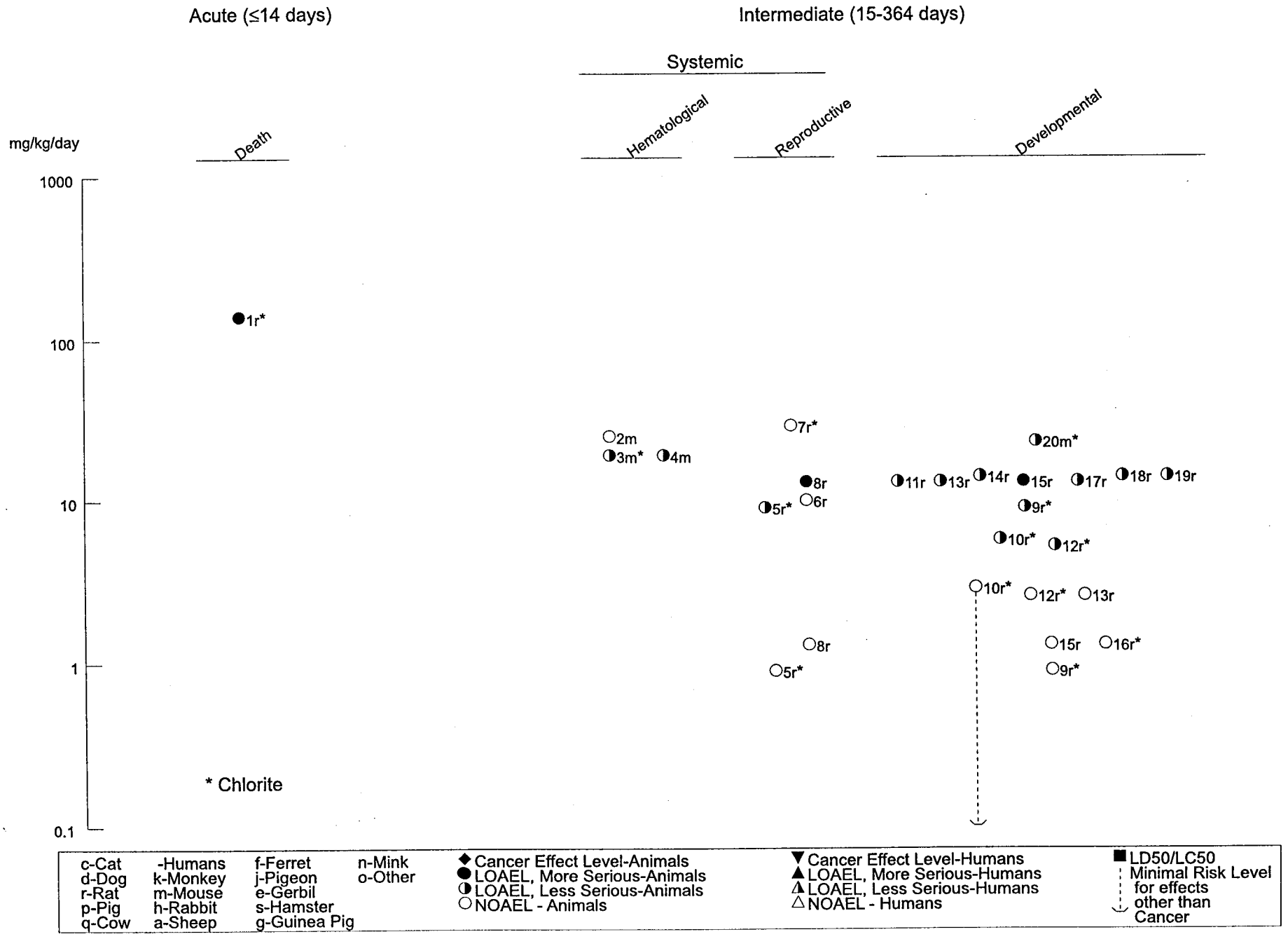
Key to figure[a]	Species (Strain)	Exposure/ Duration/ Frequency (Specific Route)	System	NOAEL (mg/kg/day)	LOAEL Less Serious (mg/kg/day)	LOAEL Serious (mg/kg/day)	Reference Chemical Form
	Developmental						
17	Rat (Sprague-Dawley)	8 wk (W)				13 M decreased activity, decreased brain weight and cell number	Taylor and Pfohl 1985 Chlorine dioxide
18	Rat (Sprague-Dawley)	ppd 5-20 (GW)				14 M decreased activity, decreased brain weight and DNA content	Taylor and Pfohl 1985 Chlorine dioxide
19	Rat (Long- Evans)	ppd 1-20 (GW)				14 decreased brain weight and protein content	Toth et al. 1990 Chlorine dioxide
20	Mouse A/J	6 wk (W)				23 decreased average pupweaning weight and birth-to-weaning growth rate	Moore et al. 1980b Chlorite

aThe number corresponds to entries in Figure 3-2.

b An intermediate-duration oral MRL of 0.1 mg/kg/day was derived from a NOAEL of 2.9 mg/kg/day and divided by an uncertainty factor of 30 (10 for interspecies extrapolation and 3 to account for sensitive populations).

d = day(s); F = Female; G = gavage; hr = hour(s); GW = gavage in water; LOAEL = lowest-observed-adverse-effect level; M = male; NOAEL = no-observed-adverse-effect level; ppd = post parturition day; (W) = drinking water; wk = week(s)

Figure 3-2 Levels of Significant Exposure to Chlorine Dioxide And Chlorite - Oral



Information regarding respiratory effects in orally-exposed animals is limited to a report of a significantly increased incidence of nasal lesions (goblet cell hyperplasia and inflammation of nasal turbinates) following 90 days of exposure to chlorine dioxide in the drinking water at concentrations that resulted in estimated doses as low as 2 mg/kg/day in males and 8 mg/kg/day in females (Daniel et al. 1990). These nasal effects were likely caused by inhalation of chlorine dioxide vapors released from the water rather than a systemic respiratory effect following oral exposure.

Gastrointestinal Effects. Information in humans is limited to a single account of abdominal cramps, nausea, and vomiting within a few minutes after a 25-year-old Chinese male had consumed 10 g of sodium chlorite dissolved in 100 mL of water in an apparent suicide attempt (Lin and Lim 1993).

Information regarding gastrointestinal effects in animals following oral exposure to chlorine dioxide or chlorite is also limited. Bercz et al. (1982) reported erythema and ulceration of the oral mucosa in adult African green monkeys exposed to chlorine dioxide in the drinking water for between 30 and 60 days at a concentration that resulted in a dose of approximately 9 mg/kg/day. Dose-related increased severity of salivation and histopathologic alterations in the stomach (including squamous epithelial hyperplasia, hyperkeratosis, ulceration, chronic inflammation, and edema) were observed in groups of rats administered sodium chlorite in gavage doses of 25 or 80 mg/kg/day (equivalent to 19 or 60 mg chlorite/kg/day, respectively) for 13 weeks; these effects were not seen at a dose level of 7.4 mg chlorite/kg/day (Harrington et al. 1995a).

Hematological Effects. Profound methemoglobinemia was diagnosed in a 25-year-old Chinese male after he had consumed 10 g of sodium chlorite dissolved in 100 mL of water in an apparent suicide attempt (Lin and Lim 1993). Other hematological effects, including ensuing intravascular coagulation, were likely secondary to the methemoglobinemia that persisted despite treatment with methylene blue. No indications of altered hematological parameters were seen in adult male subjects consuming chlorine dioxide in aqueous solution that resulted in a single dose of approximately 0.34 mg/kg of chlorine dioxide (Lubbers et al. 1981) or in other adult males consuming approximately 0.04 mg/kg/day for 12 weeks (EPA 1981; Lubbers et al. 1984a). The same investigators tested chlorite for adverse effects in healthy adult males, and found no evidence of hematological effects after each subject consumed of a total of 1,000 mL of a solution containing 2.4 mg/L chlorite (approximately 0.068 mg/kg) in two doses (separated by 4 hours), or in other healthy normal or glucose-6-phosphate dehydrogenase (G6PD) deficient male subjects who consumed approximately 0.04 mg/kg/day for 12 weeks (Lubbers et al. 1984a, 1984b). No

chlorine dioxide- or chlorite-induced hematological effects were seen among the inhabitants of a rural village who were exposed for 12 weeks via chlorine dioxide in the drinking water at weekly measured concentrations ranging from 0.25 to 1.11 mg/L (chlorine dioxide) or from 3.19 to 6.96 mg/L (chlorite) (Michael et al. 1981). In this epidemiological study, levels of chlorine dioxide in the drinking water before and after the treatment period were <0.05 mg/L. The chlorite level in the drinking water was 0.32 mg/L prior to chlorine dioxide treatment. At 1 and 2 weeks following cessation of treatment, chlorite levels dropped to 1.4 and 0.5 mg/L, respectively.

Some animal studies include reports of hematological effects following oral exposure to chlorine dioxide or chlorite. Abdel-Rahman and coworkers (Abdel-Rahman et al. 1984b; Couri and Abdel-Rahman 1980) exposed groups of male rats to chlorine dioxide in the drinking water, 20 hours/day for 11 or 12 months, at concentrations that resulted in estimated doses of 0.1, 1, 10, and 100 mg/kg/day. Abdel-Rahman et al. (1984b) noted that several hematological parameters were significantly altered in exposed rats, relative to controls, and included decreased osmotic fragility in the 10 and 100 mg/kg/day groups after 2, 4, 7, or 9 months of exposure, and in the 1 mg/kg/day group after 9 months of exposure; decreased erythrocyte counts in the 0.1 mg/kg/day and 100 mg/kg/day groups after 9 months of exposure, but not after 7 months; reduced hematocrit and hemoglobin levels in all groups at 9 months that did not exhibit clear dose-response patterns; increased hematocrit levels in the 10 and 100 mg/kg/day groups at 7 months; and increased mean corpuscular hemoglobin concentrations in the 10 and 100 mg/kg/day groups after 9 months. The study authors suggested that the decreased osmotic fragility may have been related to the disulfide bond between hemoglobin and the cell membrane as the result of oxidative stress. Couri and Abdel-Rahman (1980) found significant increases in blood glutathione reductase levels in rats of the 1, 10, and 100 mg/kg/day groups after 6 months of exposure. At 12 months of exposure, the blood glutathione reductase levels in all exposure groups were similar to those of controls, but the levels of blood glutathione peroxidase were significantly increased at 10 and 100 mg/kg/day. Blood catalase levels were increased in the 100 mg/kg/day group after 6 and 12 months of exposure and decreased in the 0.1 and 1 mg/kg/day groups after 6 months of exposure.

Abdel-Rahman and coworkers (Abdel-Rahman et al. 1984b; Couri and Abdel-Rahman 1980) also exposed male rats to sodium chlorite in the drinking water, 20 hours/day for up to 1 year, at concentrations that resulted in estimated doses of 1 or 10 mg/kg/day. Both dose levels resulted in increased mean corpuscular hemoglobin concentration (after 7, but not 9 months) and decreased osmotic fragility after 7–9 months). Erythrocyte glutathione levels were significantly decreased at dose levels

$0.1 mg/kg/day by the end of the 1-year exposure period. No consistent treatment-related alterations in erythrocyte count, hematocrit, or hemoglobin levels were observed.

Harrington et al. (1995a) administered sodium chlorite to rats by gavage for 13 weeks, resulting in chlorite doses of 7.4, 19, or 60 mg/kg/day. Relative to controls, significant treatment-related hematological effects included decreased hematocrit and hemoglobin levels (high-dose males), increased methemoglobin and neutrophil levels (mid- and high-dose males), decreased lymphocyte count (mid-dose males), decreased mean erythrocyte count (high-dose males and females), morphological changes in erythrocytes (high-dose males and females), and increased spleen weights (high-dose males and mid- and high-dose females). An unexplained decrease in methemoglobin was observed in high-dose females.

No consistent alterations in hematological parameters (erythrocyte and total and differential leukocyte counts, hemoglobin levels, hematocrit, mean corpuscular volume) were observed in groups of male and female rats given chlorine dioxide in the drinking water for 90 days at concentrations that resulted in doses as high as 12 and 15 mg/kg/day for males and females, respectively (Daniel et al. 1990).

No significant alterations in hematological parameters were seen in adult African green monkeys given chlorine dioxide in the drinking water for up to 60 days at rising concentrations that resulted in estimated doses as high as 9 mg/kg/day (Bercz et al. 1982). Bercz and coworkers later exposed these same monkeys to sodium chlorite in the drinking water in rising concentrations that resulted in estimated chlorite doses as high as 58.4 mg/kg/day. Statistically significant dose-related hematological alterations in these monkeys included decreased erythrocyte levels and cell indices, decreased hemoglobin levels, and slight increases in reticulocyte and methemoglobin levels. However, the data were not presented in a manner that would allow identification of threshold doses for these effects.

Moore and Calabrese (1982) found no significant alterations in hematological parameters within groups of mice exposed to chlorine dioxide in the drinking water for 30 days, at a concentration that resulted in an estimated dose of 25 mg/kg/day. However, when similarly examining the hematotoxicity of chlorite, Moore and Calabrese (1982) found significant increases in mean corpuscular volume and osmotic fragility at a dose level of 19 mg/kg/day.

Heffernan et al. (1979b) observed significant methemoglobinemia within 1–2 hours in cats that had been administered chlorite in single doses of 20 or 64 mg/kg. These same investigators found no signs of

methemoglobinemia in rats exposed to sodium chlorite in the drinking water for 30–90 days at concentrations that resulted in estimated chlorite doses as high as 50 mg/kg/day. Doses $10 mg/kg/day resulted in slight anemia at 30 days, but this condition appeared to improve at 60 and 90 days.

Hepatic Effects. No indications of adverse hepatic effects (assessed in tests of serum chemistry) were seen in adult male subjects consuming chlorine dioxide in aqueous solution that resulted in a dose of approximately 0.34 mg/kg (Lubbers et al. 1981) or in other adult males consuming approximately 0.04 mg/kg/day for 12 weeks (Lubbers et al. 1984a). The same investigators administered chlorite to healthy adult males, and found no evidence of adverse hepatic effects after each subject had consumed of a total of 1,000 mL of a solution containing 2.4 mg/L chlorite (approximately 0.068 mg/kg) in two doses (separated by 4 hours), or in other healthy normal or G6PD deficient male subjects who had consumed approximately 0.04 mg/kg/day for 12 weeks (Lubbers et al. 1984a, 1984b). No chlorine dioxide- or chlorite-induced signs of altered liver function were seen among the inhabitants of a rural village who were exposed for 12 weeks via chlorine dioxide in the drinking water at weekly measured concentrations ranging from 0.25 to 1.11 mg/L (chlorine dioxide) or from 3.19 to 6.96 mg/L (chlorite) (Michael et al. 1981). In this epidemiological study, levels of chlorine dioxide in the drinking water before and after the treatment period were <0.05 mg/L. The chlorite level in the drinking water was 0.32 mg/L prior to chlorine dioxide treatment. At 1 and 2 weeks following cessation of treatment, chlorite levels dropped to 1.4 and 0.5 mg/L, respectively.

Limited information is available regarding hepatic effects in animals following oral exposure to chlorine dioxide or chlorite. Daniel et al. (1990) exposed male and female rats to chlorine dioxide in the drinking water for 90 days at concentrations that resulted in estimated doses of 1.9, 3.6, 6.2, or 11.5 mg/kg/day for males and 2.4, 4.6, 8.2, or 14.9 mg/kg/day for females. Significantly depressed mean absolute liver weights were observed in males at doses $3.6 mg/kg/day and females of the 8.2 mg/kg/day dose group. However, these groups also exhibited decreased water consumption.

Renal Effects. No chlorine dioxide- or chlorite-induced signs of altered renal function were seen among the inhabitants of a rural village who were exposed for 12 weeks via chlorine dioxide in the drinking water at weekly measured concentrations ranging from 0.25 to 1.11 mg/L (chlorine dioxide) or from 3.19 to 6.96 mg/L (chlorite) (Michael et al. 1981). In this epidemiological study, levels of chlorine dioxide in the drinking water before and after the treatment period were <0.05 mg/L. The chlorite level in the drinking water was 0.32 mg/L prior to chlorine dioxide treatment. At 1 and 2 weeks following

cessation of treatment, chlorite levels dropped to 1.4 and 0.5 mg/L, respectively. Acute renal failure developed in a 25-year-old Chinese male some days after he had consumed 10 g of sodium chlorite dissolved in 100 mL of water in an apparent suicide attempt (Lin and Lim 1993), but this effect followed earlier signs of profound methemoglobinemia and respiratory distress.

Information regarding renal effects in animals is limited. Moore and Calabrese (1982) found no evidence of renal effects in mice exposed to sodium chlorite in the drinking water for up to 180 days at a concentration that resulted in an estimated chlorite dose of 25 mg/kg/day. Haag (1949) reported treatment-related pathological effects (distension of the glomerular capsule and appearance of a pale pinkish staining material in the renal tubules) in the kidneys of rats exposed to chlorite in the drinking water for 2 years at concentrations that resulted in estimated doses of 7 or 13 mg/kg/day. Increased relative kidney weights, in the absence histopathological renal effects, were observed in rats administered sodium chlorite in gavage doses of 80 mg/kg/day (equivalent to 60 mg chlorite/kg/day) for 13 weeks (Harrington et al. 1995a).

Endocrine Effects. No reports were located in which endocrine effects could be associated with oral exposure to chlorine dioxide or chlorite in humans.

Information from animal studies is limited to accounts of significantly reduced serum levels of the T4 thyroid hormone in African green monkeys consuming approximately 9 mg chlorine dioxide/kg/day from the drinking water for 6 weeks or approximately 58.4 mg chlorite/kg/day for 8 weeks (Bercz et al. 1982), and a single report of significantly increased adrenal weight in female rats administered sodium chlorite gavage doses $25 mg/kg/day ($19 mg chlorite/kg/day) for 13 weeks (Harrington et al. 1995a). Refer to Section 3.2.2.6 for information regarding altered serum hormone levels in laboratory animals that had been exposed via their mothers during prenatal and postnatal development.

Body Weight Effects. No reports were located in which body weight effects could be associated with oral exposure to chlorine dioxide or chlorite in humans.

Abdel-Rahman et al. (1984b) reported significantly reduced body weight gain (up to 18% lower than controls) in male rats exposed to chlorine dioxide in the drinking water for 11 months at concentrations resulting in estimated doses ranging from 0.12 to 120 mg/kg/day. The same authors reported similar, but less pronounced, reduced body weight gain in rats exposed to sodium chlorite at concentrations that

resulted in chlorite doses of approximately 1.2 and 12 mg/kg/day. Although this effect appeared earlier at the highest concentration, mean terminal body weight after 11 months of exposure was lower in low-dose rats than in high-dose rats. Furthermore, the authors did not provide information regarding water and food consumption. Kurokawa et al. (1986) reported slightly decreased body weight gain (<10% lower than controls) in male and female rats exposed to sodium chlorite in the drinking water for up to 85 weeks at concentrations that resulted in estimated chlorite doses of 13.5 and 24 mg/kg/day in males and 21 and 31 mg/kg/day in females.

Harrington et al. (1995a) found no significant adverse body weight effects in rats administered up to 60 mg chlorite/kg/day (via gavage) for 13 weeks. No treatment-related effects on body weight were seen in male rats that were administered chlorine dioxide in gavage doses of 2.5, 5, or 10 mg/kg/day for 56 days prior to mating and 10 more days during mating, or in female rats administered the same doses for 14 days prior to mating and throughout mating, gestation, and lactation (Carlton et al. 1991). No significant adverse body weight effects were seen in mice given sodium chlorite in the drinking water for up to 180 days at concentrations resulting in estimated chlorite doses as high as 25 mg/kg/day (Moore and Calabrese 1982) or in other mice exposed to sodium chlorite for 80 weeks at a concentration that resulted in an estimated chlorite dose of 90 mg/kg/day (Kurokawa et al. 1986).

3.2.2.3 Immunological and Lymphoreticular Effects

No reports were located in which immunological or lymphoreticular effects could be associated with oral exposure to chlorine dioxide or chlorite in humans.

Animal data are restricted to limited accounts of treatment-related altered thymus and spleen weights. Daniel et al. (1990) observed reduced spleen weights in female, but not male, rats exposed to chlorine dioxide in the drinking water for 90 days at concentrations that resulted in estimated doses ranging from 2 to 15 mg/kg/day, but the basis for this effect was not discussed. Harrington et al. (1995a) found significantly increased spleen weights in male rats administered sodium chlorite by gavage at a dose level of 80 mg/kg/day (60 mg chlorite/kg/day) for 13 weeks and in female rats similarly treated with 10 or 60 mg chlorite/kg/day. In this study, increased spleen weights were attributed to morphological changes in erythrocytes. Significantly lower spleen and thymus weights were seen in F_1 and F_2 rats that had been exposed to sodium chlorite via their mothers during gestation and lactation and via the drinking water after weaning (Gill et al. 2000).

3.2.2.4 Neurological Effects

No reports were located in which neurological effects could be associated with oral exposure to chlorine dioxide or chlorite in humans or animals. Refer to Section 3.2.2.6 for information regarding neurodevelopmental effects.

3.2.2.5 Reproductive Effects

No reports were located in which reproductive effects could be associated with oral exposure to chlorine dioxide or chlorite in humans.

A paucity of evidence exists for reproductive effects in animals following oral exposure to chlorine dioxide or chlorite. Slight, but significantly altered sperm morphology and motility were observed in male rats exposed to sodium chlorite in the drinking water for 66–76 days at concentrations that resulted in estimated chlorite doses of 9 and 37 mg/kg/day; however, no dose-related alterations in fertility rates or reproductive tissues (both gross and histopathological examination) were seen (Carlton and Smith 1985; Carlton et al. 1987). The study of Carlton et al. (1987) identified a NOAEL of 0.9 mg/kg/day and a LOAEL of 9 mg/kg/day for decreased progressive sperm movement.

Significantly decreased testicular deoxyribonucleic acid (DNA) synthesis was noted in male rats given chlorine dioxide or chlorite (as sodium salt) in the drinking water for 3 months at concentrations that resulted in estimated chlorine dioxide and chlorite doses $1.3 and 0.13 mg/kg/day, respectively (Abdel-Rahman et al. 1984b), and other male rats exposed for 3 weeks to a concentration that resulted in a chlorine dioxide dose of 13 mg/kg/day or a chlorite dose of 1.3 mg/kg/day (Suh et al. 1983). A treatment-related decreased number of implants was noted in untreated females that had been mated with chlorine dioxide-treated males of the 13 mg/kg/day level (Suh et al. 1983), this dose level was identified as a LOAEL. No significant increases in abnormal sperm-head morphology were seen in mice given chlorine dioxide or chlorite in gavage doses as high as 16 and 40 mg/kg/day, respectively, for 5 days followed by 3 weeks without treatment prior to testing (Meier et al. 1985). Carlton et al. (1991) found no significant treatment-related effects on fertility rates or sperm parameters in rats following the administration of chlorine dioxide in gavage doses as high as 10 mg/kg/day for 56 days prior to mating and throughout a 10-day mating period (males) and 14 days prior to mating and throughout mating, gestation, and lactation (females).

Couri et al. (1982b) exposed pregnant rats to sodium chlorite in the drinking water during gestational days 8–15 at concentrations that resulted in estimated chlorite doses of 70, 440, or 610 mg/kg/day. The litters were either delivered at term or by cesarean section on gestational day 22. An increase in the number of resorbed and dead fetuses was observed in cesarean-delivered litters of all exposure levels; two litters out of five were totally resorbed in the high-dose group.

The highest NOAEL values and all LOAEL values from each reliable study for reproductive effects in each species and duration are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.6 Developmental Effects

Information regarding developmental effects in humans following oral exposure to chlorine dioxide or chlorite is limited.

Tuthill et al. (1982) retrospectively compared infant morbidity and mortality data for a community that had utilized chlorine dioxide as a drinking water disinfectant in the 1940s with data of a neighboring community that used conventional drinking water chlorination practices. Exposure to chlorine dioxide-treated water did not adversely affect fetal or perinatal mortality, or birth weight, maximum weight loss, weight loss at 6 days, sex ratio, or birth condition. The authors reported a significantly greater proportion of premature births in the community using chlorine dioxide, as judged by physician assessment. However, other measures of premature birth, such as birth weight and gestational age, did not support the results based on physician assessment. Infants from the community using chlorine dioxide exhibited statistically significantly greater maximum weight loss after birth and smaller weight gain in 6 days, although these effects appeared to be partially linked to the mode of feeding practiced by the mother.

Kanitz et al. (1996) followed 548 births at Galliera Hospital, Genoa, Italy, and 128 births at Chiavari Hospital, Chiavari, Italy, during 1988–1989. Data on infant birth weight, body length, cranial circumference, and neonatal jaundice and on maternal age, smoking, alcohol consumption, education, and preterm delivery were collected from hospital records. Women in Genoa were exposed to filtered water disinfected with chlorine dioxide, sodium hypochlorite, or both; trihalomethane levels varied from 8 to 16 ppb in sodium hypochlorite-treated water and from 1 to 3 ppb in chlorine dioxide-disinfected water. Levels of chlorine dioxide in the water immediately after treatment were <0.3 mg/L, while chlorine residue was <0.4 mg/L. Women residing in Chiavari used water pumped from wells, without any

disinfection treatment, and served as the comparison group (controls). Odds ratios (ORs) were determined for the somatic parameters by comparison of groups exposed to chlorine dioxide, sodium hypochlorite, or both with controls and adjusted for maternal education level, income, maternal age, alcohol consumption, and smoking, as well as for sex of the child. Neonatal jaundice occurred more frequently (OR=1.7; 95% confidence interval [CI]=1.1–3.1) in infants whose mothers resided in the area where surface water was disinfected with chlorine dioxide, when compared with infants with mothers using nondisinfected well water. Infants born to mothers residing in areas where surface water was disinfected had smaller cranial circumference (#35 cm) (OR=2.2, 95% CI=1.4–3.9 for chlorine dioxide; OR=3.5, 95% CI=2.1–8.5 for sodium hypochlorite vs. untreated well water; OR=2.4, 95% CI=1.6–5.3 for both vs. untreated well water). In addition, these infants had a smaller body length (#49.5 cm) (OR=2.0, 95% CI=1.2–3.3 for chlorine dioxide vs. untreated well water; OR=2.3, 95% CI=1.3–4.2 for sodium hypochlorite vs. untreated well water). Risks for low birth weight (#2,500 g) were reported to be increased among mothers residing in areas using water disinfected with chlorine dioxide, but these associations were not statistically significant. For preterm delivery (#37 weeks), small but not statistically significant increased risks were found among mothers residing in the area using chlorine dioxide. The study authors concluded that infants of women who consumed drinking water treated with chlorine compounds during pregnancy were at higher risk for neonatal jaundice, cranial circumference #35 cm, and body length #49.5 cm.

Interpretability of the results of Kanitz et al. (1996) is limited by lack of consideration of exposure and potential confounding variables such as lack of quantitative exposure information, exposure to other chemicals in the water, and nutritional habits of the women. In addition, baseline values for the infant sex ratio and percentage of low-weight births for the comparison group deviate from values presented by the World Health Organization for Italy. For example, the sex ratio (male/female live births x 100) used in the study for the comparison group was 86, but most recent data (1996; as cited in WHO 2002) for Italy indicate a sex ratio value of 106. Although the percentage of low-weight births in the control group for the Kanitz et al. (1996) study was 0.8%, the percentage of low-weight births (<2,500 g) in Italy for 1994 was 6%. The quality of the untreated well water is not known (i.e., whether it contained any chemical or biological contaminants).

Källén and Robert (2000) found no adverse effects on congenital malformations, childhood cancer, infant mortality, low Apgar score, neonatal jaundice, or neonatal hypothyroidism among infants and children who lived in areas where drinking water was disinfected with chlorine dioxide, compared to controls

living in areas where chlorination of drinking water was not practiced. This study is limited because levels of chlorination products and byproducts in the drinking water were not monitored.

Numerous animal studies are available in which developmental end points have been evaluated following oral exposure to chlorine dioxide or chlorite. Some studies cited effects such as decreases in brain weight, brain cell number, exploratory behavior, locomotor activity, and serum thyroxine levels in rat pups whose mothers were exposed to chlorine dioxide before mating and during gestation and lactation and other rat pups that were directly exposed via oral gavage only during postnatal development. Effects such as decreases in serum thyroxine levels, body weight and growth, exploratory behavior, and amplitude of auditory startle response were reported in rat pups whose mothers were exposed to chlorite before mating and during gestation and lactation.

Chlorine Dioxide. Mobley et al. (1990) administered chlorine dioxide in the drinking water of female rats for 10 days prior to mating with unexposed males, and during gestation and lactation (until postconception days 35–42) at a concentration that resulted in an estimated dose of 14 mg/kg/day. No treatment-related effects were seen in litter size at birth, pup weight gain, or day of eye opening. Litter weight at birth was significantly lower (5% lower) than controls. At ages 36 through 39 days postconception, exploratory activity was significantly depressed, relative to controls, but not on day 40. On postconception days 37 and 38, no significant treatment-related effects were seen in serum T3 or T4 levels, but T3 uptake was significantly decreased. By postconception day 42, T3 uptake in exposed pups was no longer significantly different from controls. The authors suggested that reduced T3 uptake may be the source of delay in exploratory activity. This study identified a LOAEL of 13 mg/kg/day for decreased litter weight and exploratory activity.

Orme et al. (1985) exposed rat dams to chlorine dioxide in the drinking water for 2 weeks prior to mating and throughout gestation and lactation at concentrations resulting in estimated doses of 0.26, 2.6, or 13 mg/kg/day. Maternal body weights were not significantly affected by treatment. No significant treatment-related effects were seen in pup body weights or age at eye opening. Consistent, but not significantly lower activity levels were observed in 13 mg/kg/day pups, relative to controls, on postpartum days 15–20. At 13 mg/kg/day, pups also exhibited significantly depressed serum T4 and elevated T3 levels, relative to controls, when tested on postpartum day 21. A significant correlation was noted between T4 levels and locomotor activity. This study identified a NOAEL of 2.6 mg/kg/day and a LOAEL of 13 mg/kg/day for altered serum thyroid hormone levels. In the same report, pups of

unexposed rat dams were administered chlorine dioxide in a gavage dose of 14 mg/kg/day on postnatal days 5–20. Relative to controls, treated pups exhibited lower body weights at 14 and 21 days (17 and 33% lower, respectively), lower activity levels at days 18 and 19 (but not days 15–17 and 20), and lower serum T4 levels on postpartum day 21. Age at eye opening and serum T3 levels were not significantly different from controls. A significant correlation was noted between T4 levels and locomotor activity. This study identified a LOAEL of 14 mg/kg/day for decreased activity and decreased serum T4.

Taylor and Pfohl (1985) found no significant treatment-related effects on body weights of rat pups whose mothers had been exposed to chlorine dioxide in the drinking water for 14 days prior to mating and throughout gestation and lactation at a concentration that resulted in an estimated dose of 13 mg/kg/day. Compared with controls, the treated pups exhibited consistently (but not significantly) lower activity levels (assessed at 10–20 days of age), significantly decreased whole brain weight (primarily because of a decrease in cerebellar weight) and cerebellar total DNA content (due to a decrease in total cell number) in 21-day-old pups, and decreased exploratory activity at 60 days of age. This study identified a LOAEL of 13 mg/kg/day for decreased activity and decreased brain weight and cell number. Other pups were exposed to chlorine dioxide only during postnatal days 5–20 at a daily gavage dose of 14 mg/kg. At 21 days of age, these pups exhibited significant decreases in body weight, absolute and relative whole brain and forebrain weights, and forebrain DNA content and total cell number, compared with controls. Decreased DNA content and total cell number were seen in the cerebellum and forebrain when tested at 11 days of age. This study identified a LOAEL of 14 mg/kg/day for decreased activity and decreased brain weight and DNA content.

Toth et al. (1990) administered chlorine dioxide to male and female rat pups at a daily gavage dose of 14 mg/kg on postnatal days 1–20. Examinations were performed on selected pups at ages 11, 21, and 35 days, and results were compared to control pups. Significantly lower (5–7% lower) body weights and decreased ratio of forebrain content to cerebellum weight were noted at all three examination times. Significantly lower forebrain weights were seen on days 21 and 35, along with accompanying reductions in protein content (days 21 and 35) and reduced DNA content (day 35). This study identified a LOAEL of 14 mg/kg/day for decreased brain weight and protein content.

Suh et al. (1983) administered chlorine dioxide in the drinking water of female rats for 2.5 months prior to mating with unexposed males, and during gestation days 1–20 at levels that resulted in estimated doses of 0.13, 1.3, or 13 mg/kg/day. The only reported maternal effect was a slight (but not significantly)

decreased maternal body weight gain in 1.3 and 13 mg/kg/day dams, relative to controls. Fetal effects included a significant trend for decreasing number of implants per litter and number of live fetuses per dam, and significantly increased total fetal weights and male fetal weights in the 13 mg/kg/day group, compared with controls. No significant effects were seen in crown-rump length or skeletal anomalies. This study identified a NOAEL of 1.3 mg/kg/day and a LOAEL of 13 mg/kg/day for decreased number of live fetuses.

Carlton et al. (1991) administered chlorine dioxide to rats in gavage doses of 2.5, 5, or 10 mg/kg for 56 days prior to mating and 10 days of mating (males) and 14 days prior to mating and throughout mating, gestation, and lactation (females). Relative to controls, pups in the exposure groups exhibited no significant differences in death before weaning, mean litter size, or mean body weight. Significantly lower absolute vaginal weight and vagina-to-body weight ratio were seen in F_1 females of the 10 mg/kg/day exposure group; no significant changes in reproductive organ weights were observed in F_1 males.

Chlorite. Gill et al. (2000; results previously published in CMA 1996) conducted a 2-generation study to examine reproductive, developmental, neurological, and hematological end points in rats exposed to sodium chlorite. Male and female rats (F_0) received sodium chlorite in the drinking water at concentrations that resulted in estimated chlorite doses of 3, 5.7, or 21 mg/kg/day for males and 3.9, 7.6, and 29 mg/kg/day for females. The treatment period lasted for 10 weeks prior to mating and during mating, after which males were sacrificed; exposure of females continued throughout gestation and lactation. Sodium chlorite concentrations were adjusted during lactation to maintain a constant intake during a period of increased water intake. F_1 generation pups were continued on the same treatment regimen as their parents (chlorite doses of 2.9, 6, or 23 mg/kg/day and 3.9, 8, or 29 mg/kg/day for F_1 males and females, respectively). Mating commenced at approximately 14 weeks of age to produce F_{2a} rats that were maintained through weaning on postnatal day 21. Due to a reduced number of litters in the mid-dose F_1-F_{2a} generation, the F_1 animals were remated following weaning of the F_{2a} rats to produce an F_{2b} generation. Significant alterations related to treatment at high-dose included reduced absolute and relative liver weight in F_1 males and females, reduced pup survival (increase in number of pups found dead and/or killed prematurely during lactation) and reduced body weight at birth and throughout lactation in F_1 and F_2 rats, lower thymus and spleen weight in both generations, lowered incidence of pups exhibiting normal righting reflex and with eyes open on postnatal day 15, decreased absolute brain weight for F_1 males and F_2 females, delayed sexual development in F_1 and F_2 males (preputial separation) and

females (vaginal opening), and lowered red blood cell parameters in F_1 rats. In the mid-dose groups, reduced absolute and relative liver weight in F_1 males was observed. In addition, a significant decrease in maximum response to an auditory startle stimulus was noted in mid- and high-dose groups on postnatal day 24, but not on postnatal day 60. The NOAEL of 2.6 mg/kg/day, identified in this study, served as the basis for the derivation of an intermediate-duration oral MRL for chlorite. A LOAEL was 5.7 mg/kg/day for lowered auditory startle response amplitude on postnatal day 24.

Mobley et al. (1990) exposed female rats to chlorite in the drinking water for 10 days prior to mating with unexposed males and during gestation and lactation until postnatal days 42–53 at concentrations that resulted in estimated chlorite doses of 2.6 or 5.2 mg/kg/day. Chlorite exposure did not adversely affect litter size or pup weight gain. Significant, consistent decreases in exploratory activity were observed in the 5.2 mg/kg/day group on postnatal days 36–39, but not on days 39–41. In the 2.6 mg/kg/day group, there were significant decreases in activity on days 36 and 37, but not on days 38–40. No significant alterations in serum T3 or T4 levels were observed in the pups. However, the free T4 levels were significantly increased in the 5.2 mg/kg/day group. The day of eye opening in the treatment groups was similar to that of controls. This study identified a NOAEL of 2.6 mg/kg/day and a LOAEL of 5.2 mg/kg/day for decreased exploratory activity on postnatal days 36–39.

Carlton and coworkers (Carlton and Smith, 1985; Carlton et al. 1987) exposed groups of 12 male rats to sodium chlorite in the drinking water for 56 days prior to mating and throughout a 10-day mating period. Groups of 24 female rats were also exposed to sodium chlorite for 14 days prior to mating, during the mating period, and throughout gestation and lactation. Estimated chlorite doses were 0.09, 0.9, or 9 mg/kg/day for males and 0.1, 1, or 10 mg/kg/day for females. No significant alterations in litter survival rates, median day of eye opening, or median day of observed vaginal patency were observed. Significant decreases in serum T3 and T4 levels were consistently observed in high-dose groups of F_1 males and females at postnatal days 21 and 40. This study identified a NOAEL of 0.9 mg/kg/day and a LOAEL of 9 mg/kg/day for decreased serum T3 and T4 levels in pups.

Couri et al. (1982b) exposed pregnant rats to sodium chlorite in the drinking water during gestational days 8–15 at concentrations that resulted in estimated chlorite doses of 70, 440, or 610 mg/kg/day. The litters were either delivered at term or by cesarean section on gestational day 22. Significant decreases in crown-rump length were observed at all doses in term-delivered litters and in the 70 mg/kg/day group that was cesarean-delivered. Fetal weights were not adversely affected. An increase in the number of

resorbed and dead fetuses was observed in cesarean-delivered litters of all exposure levels; two litters out of five were totally resorbed in the high-dose group. Postnatal growth and the incidences of soft tissue and skeletal malformations were not adversely affected.

Suh et al. (1983) administered chlorite in the drinking water of female rats for 2.5 months prior to mating with unexposed males and during gestational days 0–20 at chlorite concentrations that resulted in estimated doses of 0.13 or 1.3 mg/kg/day; the dams were killed on gestational day 20. No treatment-related effects were seen regarding resorptions, dead fetuses, or fetal body weights. Crown-rump length was significantly higher in the high-dose group compared with controls, but the difference was very small and is probably not biologically significant. Chlorite exposure did not significantly alter incidence of skeletal anomalies. This study identified a NOAEL of 1.3 mg/kg/day.

Moore and coworkers (Moore and Calabrese 1982; Moore et al. 1980b) exposed pregnant mice to sodium chlorite in the drinking water throughout gestation and lactation at a concentration that resulted in an estimated chlorite dose of 23 mg/kg/day. A decrease in the conception rate (number of females positive for vaginal plug/number of females producing litters; 39 vs. 56% in controls) was observed; the statistical significance was not reported. No significant alterations in gestation length, litter size, number of pups dead at birth, or number of pups alive at weaning were observed. Pup growth was adversely affected, as shown by significant decreases in average pup weaning weight and birth-to-weaning growth rate.

Harrington et al. (1995b) treated rabbits with sodium chlorite via their drinking water on gestation days 7–20 at levels that resulted in estimated chlorite doses of 10, 26, or 40 mg/kg/day. Dams were sacrificed on gestation day 28. Although the number and mean percentage of major external and visceral and skeletal abnormalities were increased in the 26 and 40 mg/kg/day groups (external/visceral: 6.6 and 2.9%, respectively, vs. 1.5% in controls; skeletal: 5.4 and 0%, respectively, vs. 0% in controls), the authors did not consider these to be treatment-related adverse effects. Mean fetal weights in the 26 and 40 mg/kg/day groups were slightly decreased (<9%, relative to controls). In the 26 and 40 mg/kg/day groups, the incidence of minor skeletal abnormalities (13.9 and 14.2% for the 26 and 40 mg/kg/day groups, respectively, vs. 7.7% in controls) and skeletal variants related to incomplete fetal bone ossification was higher than for controls. The authors state in their discussion that these alterations in fetal body weight and delayed ossification indicate embryonic growth retardation. Decreases in maternal food and water consumption and body weight gain may be responsible, at least in part, for some of the fetal effects.

Skowronski et al. (1985) administered Alcide (a liquid sterilizer consisting of sodium chlorite and lactic acid that form chlorine dioxide) to mice and rats in gavage doses of 1 and 0.1 mL, respectively, on gestation days 6–15. No signs of maternal toxicity were observed, and there were no statistically significant adverse fetal effects.

The highest NOAEL values and all LOAEL values from each reliable study for developmental effects in each species and duration are recorded in Table 3-2 and plotted in Figure 3-2.

3.2.2.7 Cancer

No reports were located in which cancer could be associated with oral exposure to chlorine dioxide or chlorite in humans.

Kurokawa et al. (1986) performed a cancer bioassay on rats and mice that were exposed to sodium chlorite in the drinking water. Rats were exposed to concentrations that resulted in estimated chlorite doses of 13.5 or 24 mg/kg/day in males and 21 or 31 mg/kg/day in females. All groups of rats became infected with the Sendai virus, causing a premature termination of the study after 85 weeks of exposure. Mice were exposed for 80 weeks to concentrations that resulted in estimated doses of 45 or 90 mg/kg/day. Mice received distilled water only for an additional 5 weeks following the 80-week treatment period. Yokose et al. (1987) also published a report of the mouse data presented in Kurokawa et al. (1986). The two accounts vary slightly in exposure duration information and in reported numbers of tumor-bearing mice at study end. Yokose et al. (1987) indicated that exposure of mice was terminated at 80 weeks according to a guideline for carcinogenicity studies from the Ministry of Health and Welfare of Japan.

No chlorite-related increased tumor incidences were observed in rats. Significant increases in liver and lung tumors were observed in the male mice. Incidence of hyperplastic nodules in the liver was significantly increased in the low- and high-dose groups relative to controls (3/35 [reported as 6/35 in Yokose et al. 1987], 14/47, and 11/43, in the control, low-, and high-dose groups, respectively) and combined incidence of liver hyperplastic nodules and hepatocellular carcinoma was increased in the low-dose group (7/35, 22/47, and 17/43, respectively). Incidence of lung adenoma (0/35, 2/47, and 5/43, respectively) and combined incidence for lung adenoma and adenocarcinoma (0/35, 3/47, and 7/43, respectively) were significantly increased in the high-dose group compared with controls. The study authors noted that incidences of liver hyperplastic nodules and lung adenomas in the treated animals were

within the range of historical controls in their laboratory and in the National Toxicology Program laboratories. In addition, high mortality in the control males because of fighting reduced the sample size, making statistical comparisons between controls and treated animals difficult to interpret. In the female mice, the only significant alteration in tumor incidence was a significantly lower incidence of malignant lymphoma/leukemia in the high-dose group (7/47, 5/50, and 1/50, respectively). The exposure durations of both rat and mouse studies were considerably less-than-lifetime exposure guidelines for adequate carcinogenicity studies.

Using three short-term assays, Miller et al. (1986) found no evidence of carcinogenic potential of drinking water disinfected with chlorine dioxide. In an initiation-promotion assay, water was disinfected with chlorine dioxide, after which water samples containing chlorine dioxide residue were concentrated and administered orally to mice 3 times/week for 2 weeks. The mice were then exposed to 12-tetra-decanylphorbal-13-acetate (a known cancer promoter) in acetone by dermal applications 3 times/week for 20 weeks. No significant increases in the number of skin tumors or the number of tumors per animal were observed, compared with vehicle controls. In a lung adenoma assay, groups of female Strain A mice received 0.25 mL gavage doses of the concentrated water samples 3 times/week for 8 weeks, followed by a 16-week observation period. The number of animals with lung adenomas and the number of adenomas per animal were not significantly altered compared with vehicle controls. In the third assay, partially hepatectomized rats were exposed to a single oral dose of the concentrated water samples followed 1week later by administration of 500 mg/L sodium phenobarbital (a known cancer promoter) in drinking water for 56 days. Examination of livers in the treated rats did not reveal significant treatment-induced increases in gamma glutamyl transpeptidase-positive foci (an indicator of preneoplastic liver changes).

3.2.3 Dermal Exposure

The database for health effects related to dermal exposure to chlorine dioxide or chlorite is extremely limited. No reports were located regarding adverse effects in humans following dermal exposure to chlorine dioxide or chlorite. Available information in animals is restricted to a report that a solution containing chlorine dioxide concentrations of approximately 9.7–11.4 mg/L was nonirritating to the skin of mice in a 48-hour test. Dermal exposure to high concentrations would be expected to result in irritation, due to the oxidizing properties of chlorine dioxide and chlorite. Sodium chlorite was not carcinogenic in mice treated dermally for 51 weeks. Nor did sodium chlorite appear to be a cancer

promoter in mice initiated with a single dermal dose of dimethylbenzanthracene followed by 51 weeks of dermal exposure to sodium chlorite.

The toxicity of Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid that produce chlorine dioxide when mixed, was assessed in laboratory animals following repeated exposure and in fetuses of pregnant animals following *in utero* exposure during critical periods of organogenesis (Abdel-Rahman et al. 1987a, 1987b; Gerges et al. 1985). However, levels of exposure to sodium chlorite and chlorine dioxide were not known and uncertainty exists regarding the potential for the formation of other reactive substances that could trigger toxic responses.

3.2.3.1 Death

No reports were located regarding death in humans or animals following dermal exposure to chlorine dioxide or chlorite.

3.2.3.2 Systemic Effects

No reports were located in which respiratory, cardiovascular, gastrointestinal, hematological, musculoskeletal, hepatic, renal, endocrine, ocular, or body weight effects could be associated with dermal exposure to chlorine dioxide or chlorite in humans or animals.

Dermal Effects. No reports were located regarding dermal effects in humans following dermal exposure to chlorine dioxide or chlorite.

A solution containing chlorine dioxide concentrations of approximately 9.7–11.4 mg/L was nonirritating to the skin of mice in a 48-hour test (Shi and Xie 1999). Moderate to severe erythema was observed in rabbits following repeated daily applications of Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid that produce chlorine dioxide when mixed (Abdel-Rahman et al. 1987b). However, levels of exposure to sodium chlorite or chlorine dioxide could not be quantified.

No reports were located in which the following health effects in humans or animals could be associated with dermal exposure to chlorine dioxide or chlorite:

3.2.3.3 Immunological and Lymphoreticular Effects

3.2.3.4 Neurological Effects

3.2.3.5 Reproductive Effects

3.2.3.6 Developmental Effects

No reports were located regarding developmental effects in humans following dermal exposure to chlorine dioxide or chlorite.

Animal data are limited to studies of laboratory rodents exposed to Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid that produce chlorine dioxide when mixed (Abdel-Rahman et al. 1987a; Gerges et al. 1985). No statistically significant treatment-related developmental effects were observed in the offspring of rats, mice, and rabbits treated daily with dermal applications of Alcide gel (as high as 2 g/kg) during the critical period of organogenesis. However, levels of exposure to sodium chlorite or chlorine dioxide could not be quantified.

3.2.3.7 Cancer

Kurokawa et al. (1984) conducted two dermal carcinogenicity assays on chlorite. In an assay designed to assess the ability of chlorite to act as a complete carcinogen, female mice were treated with dermal applications of sodium chlorite (in acetone) twice weekly for 51 weeks. Compared with controls, sodium chlorite exposure did not result in increased tumor incidence. To test the ability of chlorite to act as a tumor promoter, a single initiating dose of dimethylbenzanthracene (DMBA) was applied to the skin of mice. The DMBA application was followed by dermal applications of sodium chlorite (in acetone) twice weekly for 51 weeks. Although incidences of tumors were higher in the chlorite/acetone-exposed mice than in those receiving acetone only, the differences were not statistically significant.

3.3 GENOTOXICITY

No reports were located regarding the genotoxicity of chlorine dioxide or chlorite in humans.

The genotoxic potential of chlorine dioxide and chlorite has been assessed in a number of standard genotoxicity test systems, resulting in both positive and negative results. Chlorine dioxide tested positive

for reverse mutations in *Salmonella typhimurium* (with activation), but did not increase chromosomal aberrations in Chinese hamster fibroblast cells (Ishidate et al. 1984). Samples of water that had been disinfected with chlorine dioxide did not induce reverse mutations in *S. typhimurium* with or without activation (Miller et al. 1986). Negative results were obtained from *in vivo* assays for micronuclei and bone marrow chromosomal aberrations in Swiss CD-1 mice, as well as sperm-head abnormalities in B6C3F1 mice, following gavage administration of chlorine dioxide doses ranging from 0.1 to 0.4 mg/mouse/day for 5 consecutive days (Meier et al. 1985). Hayashi et al. (1988) reported positive results in the micronucleus assay in ddY mice following single intraperitoneal injection of chlorine dioxide at dose levels of 3.2–25 mg/kg.

Sodium chlorite induced reverse mutations in *S. typhimurium* (with activation) and chromosomal aberrations in Chinese hamster fibroblast cells (Ishidate et al. 1984). Negative results were obtained from *in vivo* assays for micronuclei and bone marrow chromosomal aberrations in Swiss CD-1 mice, as well as sperm-head abnormalities in B6C3F1 mice, following gavage administration of sodium chlorite at doses ranging from 0.25 to 1 mg/mouse/day for 5 consecutive days (Meier et al. 1985). Hayashi et al. (1988) reported negative results for induction of micronuclei in ddY mice that were administered sodium chlorite in single oral gavage doses ranging from 37.5 to 300 mg/kg, but positive results were obtained in mice subjected to single or multiple intraperitoneal injection of 7.5 to 60 mg sodium chlorite/kg.

3.4 TOXICOKINETICS

Although no data were located regarding absorption following inhalation exposure to chlorine dioxide, little absorption of parent compound across lung tissue would be expected due to the highly reactive nature of chlorine dioxide. The rapid appearance of ^{36}Cl in plasma following oral administration of chlorine dioxide ($^{36}ClO_2$) or chlorite ($^{36}ClO_2^-$) has been shown in laboratory animals. Using 72-hour urinary excretion rates for ^{36}Cl, absorption rates of 30–35% of intragastrically administered chlorine dioxide or chlorite have been estimated. Limited animal data indicate the presence of ^{36}Cl in plasma following dermal application of Alcide, an antimicrobial compound containing sodium chlorite and lactic acid that rapidly form chlorine dioxide when mixed together. In rats, absorbed ^{36}Cl (from $^{36}ClO_2$ or $^{36}ClO_2^-$ exposure sources) is slowly cleared from the blood and is widely distributed throughout the body. Chlorine dioxide rapidly dissociates, predominantly into chlorite (which itself is highly reactive) and chloride ion (Cl^-), ultimately the major metabolite of both chlorine dioxide and chlorite in biological systems. Urine is the primary route of ^{36}Cl elimination, predominantly in the form of chloride ion.

3.4.1 Absorption

3.4.1.1 Inhalation Exposure

No information was located regarding absorption following inhalation exposure to chlorine dioxide or chlorite in humans or animals.

3.4.1.2 Oral Exposure

No information was located regarding absorption following oral exposure to chlorine dioxide or chlorite in humans.

In rats, a single gavage dose of $^{36}ClO_2$ resulted in the rapid appearance of ^{36}Cl in the plasma, which peaked 1 hour after dosing (Abdel-Rahman et al. 1980a). Based on 72-hour urinary excretion of 30% of the ^{36}Cl in the administered dose, it can be assumed that absorption was at least 30%. The absorption rate constant and half-time were 3.77/hour and 0.18 hours, respectively (Abdel-Rahman et al. 1982). Similar results were reported following single gavage dosing of rats with $^{36}ClO_2^-$ (Abdel-Rahman et al. 1984a). In this study, peak plasma levels of ^{36}Cl were reached within 2 hours following dosing and 72-hour urinary excretion data indicated that at least 35% of the radiolabel had been absorbed. The absorption rate constant and half-time were 0.198/hour and 3.5 hours, respectively.

3.4.1.3 Dermal Exposure

No information was located regarding absorption following dermal exposure to chlorine dioxide or chlorite in humans.

Dermal absorption of ^{36}Cl was measured in rats following 10 daily applications of Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid that produce chlorine

dioxide when mixed (Scatina et al. 1983). Maximal levels of plasma ^{36}Cl were reached after 72 hours. The absorption rate constant and half-life were 0.0314/hour and 22.1 hours, respectively.

3.4.2 Distribution

3.4.2.1 Inhalation Exposure

No information was located regarding distribution of chlorine dioxide, chlorite, or their metabolites following inhalation exposure in humans or animals.

3.4.2.2 Oral Exposure

No information was located regarding distribution of chlorine dioxide, chlorite, or their metabolites following oral exposure in humans.

Animal data indicate that ^{36}Cl, absorbed from the gastrointestinal tract following single oral (gavage) administration of $^{36}ClO_2$, is cleared from the blood with a half-time of elimination of 43.9 hours (Abdel-Rahman et al. 1982) and is widely distributed throughout the body (Abdel-Rahman et al. 1980a, 1980b, 1982, 1984a). At 72 hours following dosing, highest concentrations were found in the blood, stomach, and small intestines. Relatively high concentrations were also seen in the lung, kidney, liver, testes, spleen, thymus, and bone marrow. A shorter elimination half-time (31.0 hours) was noted in rats that had been exposed to chlorine dioxide in the drinking water for 2 weeks prior to receiving a single gavage dose of $^{36}ClO_2$ (Abdel-Rahman et al. 1980a). Single oral (gavage) administration of chlorite ($^{36}ClO_2^-$) resulted in an elimination half-time of 35.2 hours from the blood and widespread distribution of ^{36}Cl (Abdel-Rahman et al. 1982, 1984a), similar to that observed following oral exposure to chlorine dioxide.

3.4.2.3 Dermal Exposure

No information was located regarding distribution of chlorine dioxide, chlorite, or their metabolites following dermal exposure in humans or animals. However, ^{36}Cl has been measured in plasma of rats following 10 daily applications of Alcide, an antimicrobial compound consisting of solutions of sodium chlorite and lactic acid that produce chlorine dioxide when mixed (Scatina et al. 1983).

3.4.3 Metabolism

3.4.3.1 Inhalation Exposure

No information was located regarding metabolism of chlorine dioxide or chlorite following inhalation exposure in humans or animals.

3.4.3.2 Oral Exposure

Both chlorine dioxide and chlorite are primarily metabolized to chloride ion. At 72 hours following single oral (gavage) administration of radiolabeled chlorine dioxide in rats, chloride ion accounted for approximately 87% of the radioactivity that had been collected in the urine and 80% of the radioactivity in a plasma sample (Abdel-Rahman et al. 1980b). Chlorite was the other major metabolite, accounting for approximately 11 and 21% of the radioactivity in the urine and plasma samples, respectively. Chlorate was a minor component of the radioactivity in the urine. Similarly, chloride ion accounted for approximately 85% of the radioactivity in the 72-hour urine collection of rats that had been orally administered radiolabeled chlorite; the remainder in the form of chlorite (Abdel-Rahman et al. 1984a).

Both chlorine dioxide and chlorite, being strong oxidizing agents, are most likely rapidly reduced in biological systems mainly to chloride ion. Bercz et al. (1982) demonstrated this reduction for chlorine dioxide that was introduced into saliva obtained from anesthetized monkeys.

3.4.3.3 Dermal Exposure

No information was located regarding metabolism of chlorine dioxide or chlorite following dermal exposure in humans or animals.

3.4.4 Elimination and Excretion

3.4.4.1 Inhalation Exposure

No information was located regarding elimination or excretion following inhalation exposure to chlorine dioxide or chlorite in humans or animals.

3.4.4.2 Oral Exposure

The urine is the primary route of excretion of orally administered radioactivity from radiolabeled chlorine dioxide or chlorite. In rats, 72 hours following single oral (gavage) administration of $^{36}ClO_2$, 31 and 4.5% of the radiolabel had been excreted in the urine and feces, respectively, mainly in the form of the chloride ion. The ratio of $^{36}Cl^-$ to $^{36}ClO_2^-$ was 4 to 1, and no parent compound was detected (Abdel-Rahman et al. 1980a, 1980b). In rats administered a single oral (gavage) dose of radiolabeled chlorite, 35 and 5% of the radiolabel were excreted in the urine and feces, respectively, in the first 72 hours after dosing. Approximately 90% of the urinary label was in the form of chloride ion (Abdel-Rahman et al. 1984a).

3.4.4.3 Dermal Exposure

Urinary excretion of ^{36}Cl was observed in rats that had been administered Alcide, an antimicrobial compound consisting of sodium chlorite and lactic acid that form chlorine dioxide when mixed (Scatina et al. 1984). The rats had received 10 daily dermal applications, followed by an application of radiolabeled Alcide. Urinary excretion was greatest in the first 24 hours post application; the half-time of urinary elimination was 64 hours. The excreted radioactivity consisted of approximately equal portions of chloride ion and chlorite. No radioactivity was detected in feces or expired air.

3.4.5 Physiologically Based Pharmacokinetic (PBPK)/Pharmacodynamic (PD) Models

Physiologically based pharmacokinetic (PBPK) models use mathematical descriptions of the uptake and disposition of chemical substances to quantitatively describe the relationships among critical biological processes (Krishnan et al. 1994). PBPK models are also called biologically based tissue dosimetry models. PBPK models are increasingly used in risk assessments, primarily to predict the concentration of potentially toxic moieties of a chemical that will be delivered to any given target tissue following various

combinations of route, dose level, and test species (Clewell and Andersen 1985). Physiologically based pharmacodynamic (PBPD) models use mathematical descriptions of the dose-response function to quantitatively describe the relationship between target tissue dose and toxic end points.

PBPK/PD models refine our understanding of complex quantitative dose behaviors by helping to delineate and characterize the relationships between: (1) the external/exposure concentration and target tissue dose of the toxic moiety, and (2) the target tissue dose and observed responses (Andersen et al. 1987; Andersen and Krishnan 1994). These models are biologically and mechanistically based and can be used to extrapolate the pharmacokinetic behavior of chemical substances from high to low dose, from route to route, between species, and between subpopulations within a species. The biological basis of PBPK models results in more meaningful extrapolations than those generated with the more conventional use of uncertainty factors.

The PBPK model for a chemical substance is developed in four interconnected steps: (1) model representation, (2) model parametrization, (3) model simulation, and (4) model validation (Krishnan and Andersen 1994). In the early 1990s, validated PBPK models were developed for a number of toxicologically important chemical substances, both volatile and nonvolatile (Krishnan and Andersen 1994; Leung 1993). PBPK models for a particular substance require estimates of the chemical substance-specific physicochemical parameters, and species-specific physiological and biological parameters. The numerical estimates of these model parameters are incorporated within a set of differential and algebraic equations that describe the pharmacokinetic processes. Solving these differential and algebraic equations provides the predictions of tissue dose. Computers then provide process simulations based on these solutions.

The structure and mathematical expressions used in PBPK models significantly simplify the true complexities of biological systems. If the uptake and disposition of the chemical substance(s) is adequately described, however, this simplification is desirable because data are often unavailable for many biological processes. A simplified scheme reduces the magnitude of cumulative uncertainty. The adequacy of the model is, therefore, of great importance, and model validation is essential to the use of PBPK models in risk assessment.

PBPK models improve the pharmacokinetic extrapolations used in risk assessments that identify the maximal (i.e., the safe) levels for human exposure to chemical substances (Andersen and Krishnan 1994).

PBPK models provide a scientifically sound means to predict the target tissue dose of chemicals in humans who are exposed to environmental levels (for example, levels that might occur at hazardous waste sites) based on the results of studies where doses were higher or were administered in different species. Figure 3-3 shows a conceptualized representation of a PBPK model.

No PBPK models for exposure to chlorine dioxide or chlorite were identified.

3.5 MECHANISMS OF ACTION

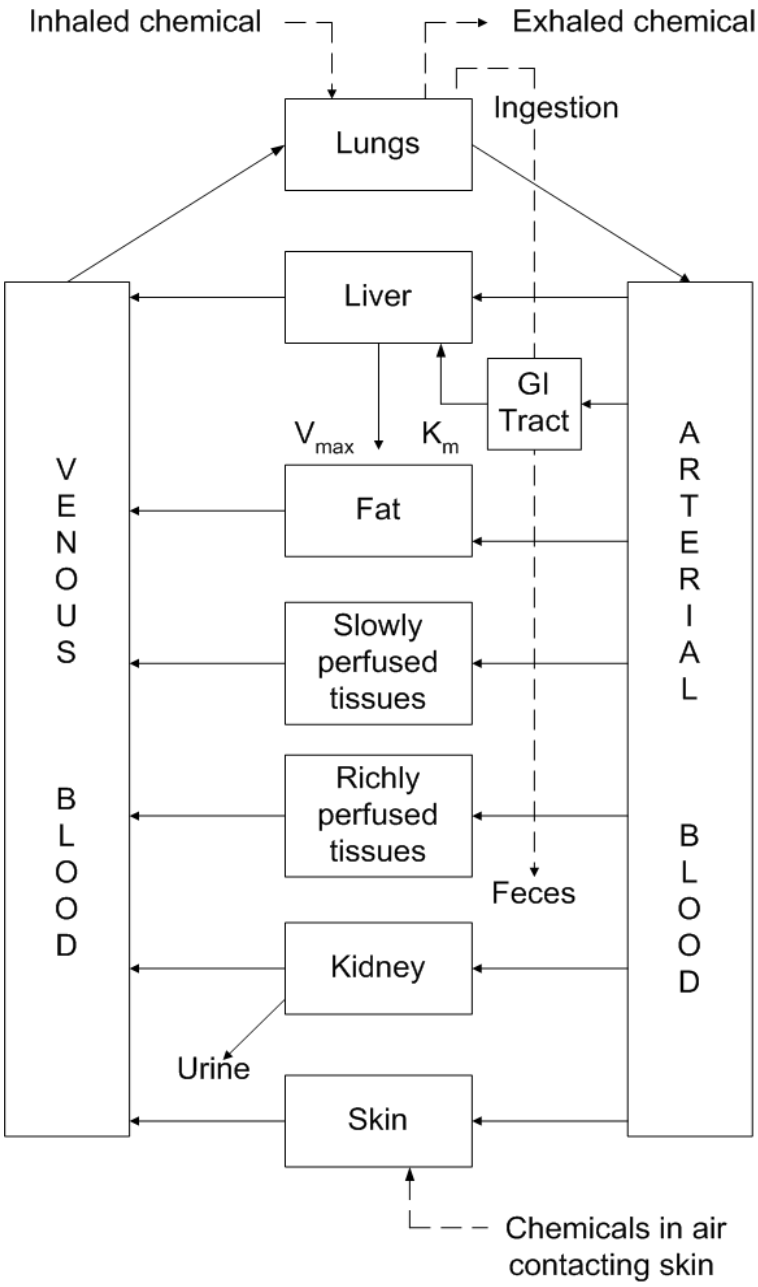
3.5.1 Pharmacokinetic Mechanisms

Absorption. No information was located regarding mechanisms of absorption of chlorine dioxide or chlorite. Being a strong oxidizer, chlorine dioxide is likely to undergo rapid redox reactions within biological tissues rather than to be absorbed as parent compound. Chlorite levels have been measured in urine following oral exposure to chlorine dioxide or chlorite, indicating that some degree of chlorite absorption occurs across the digestive tract. Due to the highly reactive nature of chlorite, itself a strong oxidizer, absorption would be expected to occur via passive diffusion rather than active transport mechanisms.

Distribution. No information was located regarding the transport of chlorine dioxide or chlorite in the blood. However, based on the fact that the strong oxidizing property of chlorine dioxide likely results in rapid conversion to chlorite (also a strong oxidizer) in biological systems, and ultimately to chloride ion, it would be expected that distribution would follow normal ionic distribution patterns.

Metabolism. Although no information was located regarding mechanisms of chlorine dioxide and chlorite metabolism, ultimate transformation to chloride ions is likely achieved via redox reactions with a variety of substances in biological systems that are readily oxidized.

Figure 3-3. Conceptual Representation of a Physiologically Based Pharmacokinetic (PBPK) Model for a Hypothetical Chemical Substance



Source: adapted from Krishnan et al. 1994

Note: This is a conceptual representation of a physiologically based pharmacokinetic (PBPK) model for a hypothetical chemical substance. The chemical substance is shown to be absorbed via the skin, by inhalation, or by ingestion, metabolized in the liver, and excreted in the urine or by exhalation.

Excretion. No information was located regarding specific mechanisms of excretion of chlorine dioxide, chlorite, or their metabolites. However, since chloride ion is the primary excretory product of chlorine dioxide and chlorite, excretory mechanisms would be expected to be similar to those responsible for excretion of other ions.

3.5.2 Mechanisms of Toxicity

Chlorine dioxide and chlorite are strong oxidizing agents that readily react upon direct contact with biological tissues, resulting in local irritation. Mechanisms whereby chlorine dioxide and chlorite exert hematological effects such as methemoglobinemia in humans (Lin and Lim 1993; Michael et al. 1981) and animals (Bercz et al. 1982; Harrington et al. 1995a; Heffernan et al. 1979b) and alterations in other blood factors are not presently known, but may be related to their properties as oxidants. Due to its highly reactive nature, it is unlikely that chlorine dioxide would be absorbed in quantities large enough to produce systemic toxicity directly. Chlorite is produced and absorbed following oral exposure to chlorine dioxide in animals (Abdel-Rahman et al. 1980b), and may be more likely to be involved in observed hematological effects than chlorine dioxide itself. Chlorite has been shown to be more efficient than chlorine dioxide in the production of methemoglobin, in decreasing blood glutathione, and in alteration of erythrocytes (Abdel-Rahman et al. 1980a, 1984b; Couri and Abdel-Rahman 1980; Heffernan et al. 1979a, 1979b). *In vitro* studies have further shown that sufficient amounts of glutathione may prevent chlorine dioxide-induced osmotic fragility, presumably by the prevention of the formation of disulfide bonds between hemoglobin and components of the cell membrane (Abdel-Rahman et al. 1984b).

Although changes in thyroid hormones have been reported in laboratory animals that were either directly exposed to chlorine dioxide or exposed to chlorine dioxide or chlorite via their mothers during pre and postpartum development (Bercz et al. 1982; Carlton and Smith 1985; Carlton et al. 1987, 1991; Mobley et al. 1990; Orme et al. 1985), possible mechanisms that might mediate such effects have not been elucidated. Increased levels of iodine have been noted in esophagus and small intestine of rats up to 24 hours after administration of gavage doses of radiolabeled iodine followed by chlorine dioxide (Harrington et al. 1985). However, no concurrent treatment-related alterations in blood or thyroid gland iodine level were seen. Because the extent of thyroid uptake of bioavailable iodine does not appear to decrease following oral exposure to chlorine dioxide, Bercz et al. (1986) speculated that indications of altered hormonogenesis, such as altered serum thyroid hormone, could be the result of absorption of

iodinated molecules having thyromimetic or thyroid inhibitory properties. These results, however, do not imply that the effect is mediated through a hormonal pathway.

Likewise, mechanisms responsible for the developmental effects observed in laboratory animals exposed to chlorine dioxide or chlorite are not known. They might be related to the oxidative properties of these chemicals. Although overt signs of neurodevelopmental effects (delays in exploratory activity and general locomotor activity) and altered serum thyroid hormone have been observed concurrently in animals that had been exposed via their mothers during pre and postpartum development, a mechanistic basis has not been investigated.

3.5.3 Animal-to-Human Extrapolations

Mechanisms involved in chlorine dioxide- and chlorite-induced oxidative stress, such as methemoglobinemia in humans and animals, would be expected to be similar across species. However, the database of pharmacokinetic and health effects information for chlorine dioxide or chlorite does not include studies in which interspecies comparisons were made.

3.6 TOXICITIES MEDIATED THROUGH THE NEUROENDOCRINE AXIS

Recently, attention has focused on the potential hazardous effects of certain chemicals on the endocrine system because of the ability of these chemicals to mimic or block endogenous hormones. Chemicals with this type of activity are most commonly referred to as *endocrine disruptors*. However, appropriate terminology to describe such effects remains controversial. The terminology *endocrine disruptors*, initially used by Colborn and Clement (1992), was also used in 1996 when Congress mandated the Environmental Protection Agency (EPA) to develop a screening program for "...certain substances [which] may have an effect produced by a naturally occurring estrogen, or other such endocrine effect[s]...". To meet this mandate, EPA convened a panel called the Endocrine Disruptors Screening and Testing Advisory Committee (EDSTAC), which in 1998 completed its deliberations and made recommendations to EPA concerning *endocrine disruptors.* In 1999, the National Academy of Sciences released a report that referred to these same types of chemicals as *hormonally active agents*. The terminology *endocrine modulators* has also been used to convey the fact that effects caused by such chemicals may not necessarily be adverse. Many scientists agree that chemicals with the ability to disrupt or modulate the endocrine system are a potential threat to the health of humans, aquatic animals, and

wildlife. However, others think that endocrine-active chemicals do not pose a significant health risk, particularly in view of the fact that hormone mimics exist in the natural environment. Examples of natural hormone mimics are the isoflavinoid phytoestrogens (Adlercreutz 1995; Livingston 1978; Mayr et al. 1992). These chemicals are derived from plants and are similar in structure and action to endogenous estrogen. Although the public health significance and descriptive terminology of substances capable of affecting the endocrine system remains controversial, scientists agree that these chemicals may affect the synthesis, secretion, transport, binding, action, or elimination of natural hormones in the body responsible for maintaining homeostasis, reproduction, development, and/or behavior (EPA 1997b). Stated differently, such compounds may cause toxicities that are mediated through the neuroendocrine axis. As a result, these chemicals may play a role in altering, for example, metabolic, sexual, immune, and neurobehavioral function. Such chemicals are also thought to be involved in inducing breast, testicular, and prostate cancers, as well as endometriosis (Berger 1994; Giwercman et al. 1993; Hoel et al. 1992).

Treatment-related altered serum thyroid hormone levels indicate that chlorine dioxide and chlorite may exert toxic effects that are mediated through the neuroendocrine axis. Changes in thyroid hormones have been reported in laboratory animals that were either directly exposed to chlorine dioxide (repeated doses as low as 9 mg/kg/day), or exposed to chlorine dioxide or chlorite via their mothers (maternal doses of chlorine dioxide and chlorite as low as 13 and 9 mg/kg/day, respectively) during pre- and postpartum development (Bercz et al. 1982; Carlton and Smith 1985; Carlton et al. 1987, 1991; Mobley et al. 1990; Orme et al. 1985).

Altered sperm morphology has been associated with oral exposure of rats to sodium chlorite at doses as low as 9 mg chlorite/kg/day for 66–76 days of exposure (Carlton and Smith 1985; Carlton et al. 1987). However, available data do not indicate that the endocrine pathway might be involved in this effect.

3.7 CHILDREN'S SUSCEPTIBILITY

This section discusses potential health effects from exposures during the period from conception to maturity at 18 years of age in humans, when all biological systems will have fully developed. Potential effects on offspring resulting from exposures of parental germ cells are considered, as well as any indirect effects on the fetus and neonate resulting from maternal exposure during gestation and lactation. Relevant animal and *in vitro* models are also discussed.

Children are not small adults. They differ from adults in their exposures and may differ in their susceptibility to hazardous chemicals. Children's unique physiology and behavior can influence the extent of their exposure. Exposures of children are discussed in Section 6.6 Exposures of Children.

Children sometimes differ from adults in their susceptibility to hazardous chemicals, but whether there is a difference depends on the chemical (Guzelian et al. 1992; NRC 1993). Children may be more or less susceptible than adults to health effects, and the relationship may change with developmental age (Guzelian et al. 1992; NRC 1993). Vulnerability often depends on developmental stage. There are critical periods of structural and functional development during both prenatal and postnatal life and a particular structure or function will be most sensitive to disruption during its critical period(s). Damage may not be evident until a later stage of development. There are often differences in pharmacokinetics and metabolism between children and adults. For example, absorption may be different in neonates because of the immaturity of their gastrointestinal tract and their larger skin surface area in proportion to body weight (Morselli et al. 1980; NRC 1993); the gastrointestinal absorption of lead is greatest in infants and young children (Ziegler et al. 1978). Distribution of xenobiotics may be different; for example, infants have a larger proportion of their bodies as extracellular water and their brains and livers are proportionately larger (Altman and Dittmer 1974; Fomon 1966; Fomon et al. 1982; Owen and Brozek 1966; Widdowson and Dickerson 1964). The infant also has an immature blood-brain barrier (Adinolfi 1985; Johanson 1980) and probably an immature blood-testis barrier (Setchell and Waites 1975). Many xenobiotic metabolizing enzymes have distinctive developmental patterns. At various stages of growth and development, levels of particular enzymes may be higher or lower than those of adults, and sometimes unique enzymes may exist at particular developmental stages (Komori et al. 1990; Leeder and Kearns 1997; NRC 1993; Vieira et al. 1996). Whether differences in xenobiotic metabolism make the child more or less susceptible also depends on whether the relevant enzymes are involved in activation of the parent compound to its toxic form or in detoxification. There may also be differences in excretion, particularly in newborns who all have a low glomerular filtration rate and have not developed efficient tubular secretion and resorption capacities (Altman and Dittmer 1974; NRC 1993; West et al. 1948). Children and adults may differ in their capacity to repair damage from chemical insults. Children also have a longer remaining lifetime in which to express damage from chemicals; this potential is particularly relevant to cancer.

Certain characteristics of the developing human may increase exposure or susceptibility, whereas others may decrease susceptibility to the same chemical. For example, although infants breathe more air per

kilogram of body weight than adults breathe, this difference might be somewhat counterbalanced by their alveoli being less developed, which results in a disproportionately smaller surface area for alveolar absorption (NRC 1993).

Developmental delays have been observed in animals following exposure of their mothers to chlorine dioxide or chlorite during gestation and/or lactation. In the absence of apparent maternal toxicity, these findings suggest that parent compound or toxic metabolite can cross the placenta and that infants and children may be particularly vulnerable to chlorine dioxide- and chlorite-mediated toxic effects. It is well recognized that neurological development continues after birth and that gastrointestinal uptake of many nutrients and chemicals is greater in the neonate than in the adult.

Infants may exhibit a greater degree of methemoglobinemia than adults following oral exposure to chlorine dioxide or chlorite because infants form methemoglobin more readily than adults, due at least in part to the presence of hemoglobin F at birth, which is readily oxidized to methemoglobin. Additional indications that infants may exhibit increased susceptibility to hematological effects of chlorine dioxide or chlorite exposure include a lower capacity to enzymatically reduce methemoglobin and a characteristically lower level of vitamin E (an important antioxidant) at birth.

No information was located regarding age-related differences in toxicokinetic parameters for chlorine dioxide or chlorite.

3.8 BIOMARKERS OF EXPOSURE AND EFFECT

Biomarkers are broadly defined as indicators signaling events in biologic systems or samples. They have been classified as markers of exposure, markers of effect, and markers of susceptibility (NAS/NRC 1989).

Due to a nascent understanding of the use and interpretation of biomarkers, implementation of biomarkers as tools of exposure in the general population is very limited. A biomarker of exposure is a xenobiotic substance or its metabolite(s) or the product of an interaction between a xenobiotic agent and some target molecule(s) or cell(s) that is measured within a compartment of an organism (NAS/NRC 1989). The preferred biomarkers of exposure are generally the substance itself or substance-specific metabolites in readily obtainable body fluid(s), or excreta. However, several factors can confound the use and interpretation of biomarkers of exposure. The body burden of a substance may be the result of exposures

from more than one source. The substance being measured may be a metabolite of another xenobiotic substance (e.g., high urinary levels of phenol can result from exposure to several different aromatic compounds). Depending on the properties of the substance (e.g., biologic half-life) and environmental conditions (e.g., duration and route of exposure), the substance and all of its metabolites may have left the body by the time samples can be taken. It may be difficult to identify individuals exposed to hazardous substances that are commonly found in body tissues and fluids (e.g., essential mineral nutrients such as copper, zinc, and selenium). Biomarkers of exposure to chlorine dioxide and chlorite are discussed in Section 3.8.1.

Biomarkers of effect are defined as any measurable biochemical, physiologic, or other alteration within an organism that, depending on magnitude, can be recognized as an established or potential health impairment or disease (NAS/NRC 1989). This definition encompasses biochemical or cellular signals of tissue dysfunction (e.g., increased liver enzyme activity or pathologic changes in female genital epithelial cells), as well as physiologic signs of dysfunction such as increased blood pressure or decreased lung capacity. Note that these markers are not often substance specific. They also may not be directly adverse, but can indicate potential health impairment (e.g., DNA adducts). Biomarkers of effects caused by chlorine dioxide and chlorite are discussed in Section 3.8.2.

A biomarker of susceptibility is an indicator of an inherent or acquired limitation of an organism's ability to respond to the challenge of exposure to a specific xenobiotic substance. It can be an intrinsic genetic or other characteristic or a preexisting disease that results in an increase in absorbed dose, a decrease in the biologically effective dose, or a target tissue response. If biomarkers of susceptibility exist, they are discussed in Section 3.10 “Populations That Are Unusually Susceptible”.

3.8.1 Biomarkers Used to Identify or Quantify Exposure to Chlorine Dioxide and Chlorite

Chlorine dioxide is a strong oxidizing agent that is not likely to be widely distributed in biological systems or excreted as parent compound. Chlorite may be detected in tissues, blood, urine, and feces, which may serve as an indication of exposure to chlorine dioxide or chlorite. However, no information was located regarding the quantification of exposure based on measured levels of chlorite in biological samples.

3.8.2 Biomarkers Used to Characterize Effects Caused by Chlorine Dioxide and Chlorite

Exposure to relatively high levels of chlorine dioxide or chlorite may result in increased methemoglobin levels. However, this effect is not unique to chlorine dioxide or chlorite. Presently, no chemical-specific biomarkers of effect are known to exist for chlorine dioxide or chlorite.

3.9 INTERACTIONS WITH OTHER CHEMICALS

No information was located regarding interactions of chlorine dioxide or chlorite with other chemicals that might impact toxicity.

3.10 POPULATIONS THAT ARE UNUSUALLY SUSCEPTIBLE

A susceptible population will exhibit a different or enhanced response to chlorine dioxide or chlorite than will most persons exposed to the same level of chlorine dioxide or chlorite in the environment. Reasons may include genetic makeup, age, health and nutritional status, and exposure to other toxic substances (e.g., cigarette smoke). These parameters result in reduced detoxification or excretion of chlorine dioxide or chlorite, or compromised function of organs affected by chlorine dioxide or chlorite. Populations who are at greater risk due to their unusually high exposure to chlorine dioxide or chlorite are discussed in Section 6.7, Populations With Potentially High Exposures.

Individuals with glucose-6-phosphate dehydrogenase (G6PD) deficiency may be more sensitive to chlorine dioxide or chlorite (Michael et al. 1981) because of a reduced capacity for maintaining significant levels of glutathione, which can lead to destruction of red blood cells and hemolytic anemia. Approximately 10% of the African American population expresses G6PD deficiency. Moore and Calabrese (1980a) demonstrated that G6PD-deficient human red blood cells exposed to chlorite exhibited markedly greater decreased glutathione and G6PD activity and increased methemoglobin levels than red blood cells from humans with normal G6PD activity. Abdel-Rahman and coworkers (Abdel-Rahman et al. 1984b; Couri and Abdel-Rahman 1980) noted decreased glutathione levels in rats chronically exposed to chlorite in the drinking water. Individuals who are deficient in NADH-dependent methemoglobin reductase, the principal means by which methemoglobin is reduced to hemoglobin, may exhibit a decreased ability to reduce methemoglobin.

Refer to Section 3.7 for information regarding age-related differences in susceptibility to chlorine dioxide and chlorite.

3.11 METHODS FOR REDUCING TOXIC EFFECTS

This section will describe clinical practice and research concerning methods for reducing toxic effects of exposure to chlorine dioxide or chlorite. However, because some of the treatments discussed may be experimental and unproven, this section should not be used as a guide for treatment of exposures to chlorine dioxide or chlorite. When specific exposures have occurred, poison control centers and medical toxicologists should be consulted for medical advice. Standard texts that discuss treatment of toxicologic emergencies contained no information concerning chlorine dioxide or chlorite.

3.11.1 Reducing Peak Absorption Following Exposure

No information was located regarding methods to reduce peak absorption following exposure to potentially toxic levels of chlorine dioxide or chlorite.

3.11.2 Reducing Body Burden

No information was located regarding methods to reduce body burden following exposure to potentially toxic levels of chlorine dioxide or chlorite. Chlorine dioxide is rapidly converted to chlorite and chloride ion in biological systems. Chlorite is fairly rapidly excreted in the urine following exposure to chlorine dioxide or chlorite. Increasing urinary output might be an effective method for reducing body burden shortly following exposure.

3.11.3 Interfering with the Mechanism of Action for Toxic Effects

Intravenous administration of methylene blue may be an effective method for reducing chlorine dioxide- or chlorite-induced increases in methemoglobin. However, this treatment is not effective in G6PD-deficient individuals.

3.12 ADEQUACY OF THE DATABASE

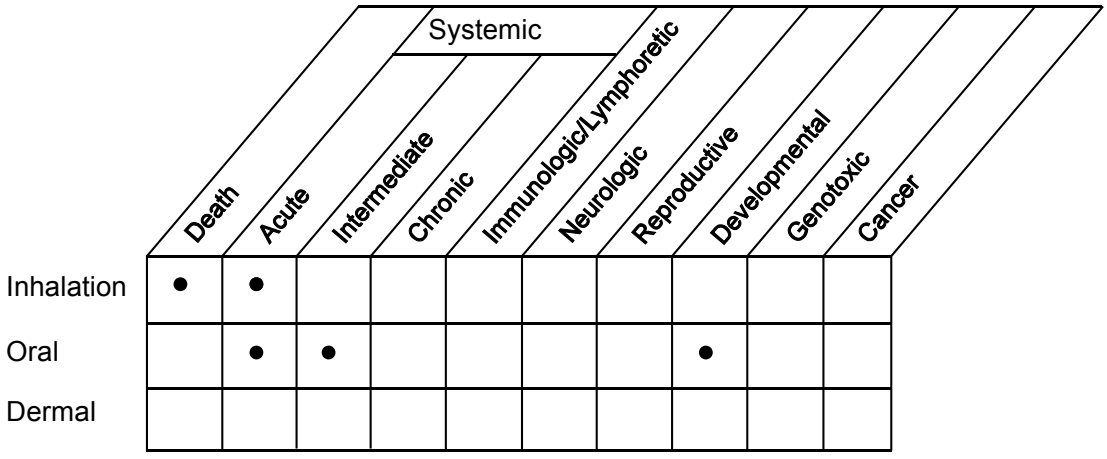
Section 104(I)(5) of CERCLA, as amended, directs the Administrator of ATSDR (in consultation with the Administrator of EPA and agencies and programs of the Public Health Service) to assess whether adequate information on the health effects of chlorine dioxide and chlorite is available. Where adequate information is not available, ATSDR, in conjunction with the National Toxicology Program (NTP), is required to assure the initiation of a program of research designed to determine the health effects (and techniques for developing methods to determine such health effects) of chlorine dioxide and chlorite.

The following categories of possible data needs have been identified by a joint team of scientists from ATSDR, NTP, and EPA. They are defined as substance-specific informational needs that if met would reduce the uncertainties of human health assessment. This definition should not be interpreted to mean that all data needs discussed in this section must be filled. In the future, the identified data needs will be evaluated and prioritized, and a substance-specific research agenda will be proposed.

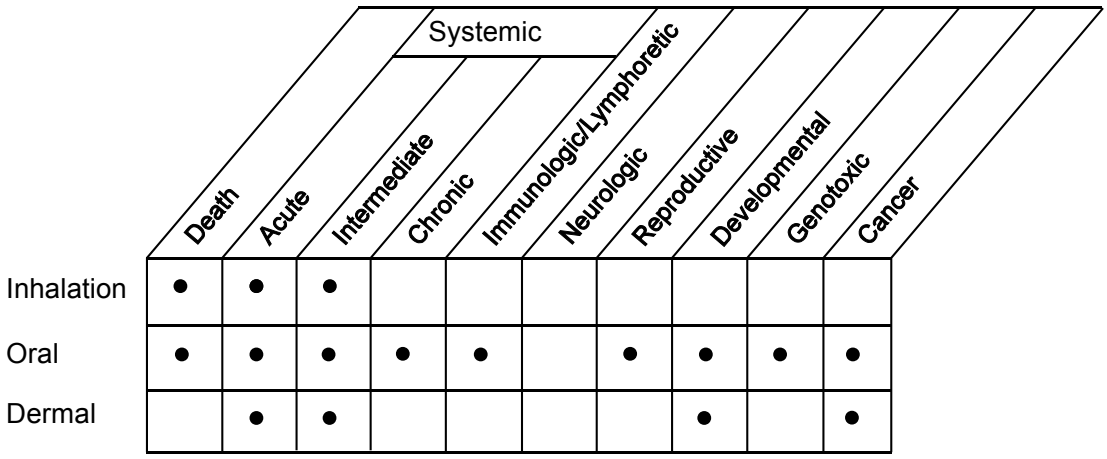
3.12.1 Existing Information on Health Effects of Chlorine Dioxide and Chlorite

The existing data on health effects of inhalation, oral, and dermal exposure of humans and animals to chlorine dioxide and chlorite are summarized in Figure 3-4. The purpose of this figure is to illustrate the existing information concerning the health effects of chlorine dioxide and chlorite. Each dot in the figure indicates that one or more studies provide information associated with that particular effect. The dot does not necessarily imply anything about the quality of the study or studies, nor should missing information in this figure be interpreted as a "data need". A data need, as defined in ATSDR's *Decision Guide for Identifying Substance-Specific Data Needs Related to Toxicological Profiles* (Agency for Toxic Substances and Disease Registry 1989), is substance-specific information necessary to conduct comprehensive public health assessments. Generally, ATSDR defines a data gap more broadly as any substance-specific information missing from the scientific literature.

Figure 3-4. Existing Information on Health Effects of Chlorine Dioxide and Chlorite



Human



Animal

- Existing Studies

3.12.2 Identification of Data Needs

Acute-Duration Exposure. Chlorine dioxide and chlorite are strong oxidizing agents that readily react upon direct contact with biological tissues, resulting in local irritation. Information regarding health effects in acutely exposed humans is limited to cases of accidental exposure to concentrated chlorine dioxide vapors (Elkins 1959; Exner-Freisfeld et al. 1986; Meggs et al. 1996) and a single case of intentional ingestion of sodium chlorite in an apparent suicide attempt (Lin and Lim 1993). Reports of acute toxicity in animals primarily concern lethality following relatively high-level inhalation or oral exposure to chlorine dioxide or chlorite (Couri et al. 1982b; Dalhamn 1957; Haller and Northgraves 1955; Harrington et al. 1995a; Musil et al. 1964; Seta et al. 1991; Shi and Xie 1999; Sperling 1959). Additional acute toxicity studies should focus on oral and inhalation exposures that result in less serious critical effects. Results of such studies might serve as bases for establishing acute-duration oral and inhalation MRLs.

Intermediate-Duration Exposure. No human studies were located regarding chlorine dioxide- or chlorite-induced adverse health effects following intermediate-duration exposure. Animal studies indicate that the respiratory system is the major target of toxicity following inhalation exposure (Dalhamn 1957; Paulet and Desbrousses 1970, 1972, 1974). The studies of Paulet and Desbrousses served as the basis for an intermediate-duration inhalation MRL. Additional animal studies should be designed to assess the effects of chlorine dioxide vapors on upper respiratory tissues, which may be more sensitive than pulmonary tissues. Intermediate-duration oral studies identified neurodevelopmental delay and thyroid hormone effects as the most sensitive chlorine dioxide- or chlorite-induced end points (Carlton and Smith 1985; Carlton et al. 1987; Gill et al. 2000; Mobley et al. 1990; Orme et al. 1985; Taylor and Pfohl 1985; Toth et al. 1990). Additional studies could be designed to further assess these critical end points and to determine whether they might be interrelated. See Section 3.12.2 for additional information concerning potential for chlorine dioxide- or chlorite-induced neurodevelopmental effects following intermediate-duration oral exposure to chlorine dioxide or chlorite.

Chronic-Duration Exposure and Cancer. No information was located regarding health effects in humans following chronic-duration exposure to chlorine dioxide or chlorite; however, information is available from animal studies (Haag 1949; Kurokawa et al. 1986). Results of animal carcinogenicity testing are available for oral (Kurokawa et al. 1986; Miller et al. 1986) and dermal exposure (Kurokawa et al. 1984). These results generally do not indicate a carcinogenic effect, with the exception of a report of

significantly higher incidences of liver and lung tumors in male mice administered sodium chlorite orally (Kurokawa et al. 1986). However, high mortality in the control males (due to fighting) reduced the sample size, making statistical comparisons between controls and treated animals difficult to interpret. A well-designed cancer bioassay that includes noncancer end points might provide valuable information concerning the effects of long-term exposure to chlorine dioxide or chlorite.

Genotoxicity. No reports were located regarding the genotoxicity of chlorine dioxide or chlorite in humans. Genotoxicity tests using standard *in vivo* and *in vitro* test systems have produced mixed results (Hayashi et al. 1988; Ishidate et al. 1984; Meier et al. 1985). Both chlorine dioxide and chlorite induced reverse mutations in *S. typhimurium* (with activation). Chlorite, but not chlorine dioxide, induced chromosomal aberrations in Chinese hamster fibroblast cells. Negative results were obtained in tests for micronuclei and chromosomal aberrations in bone marrow of mice orally administered chlorine dioxide or chlorite during a period of 5 days. However, both chlorine dioxide and chlorite produced positive results for micronuclei in mice following intraperitoneal injection. Although the database for chlorine dioxide and chlorite genotoxicity is not extensive and testing has produced mixed results, additional genotoxicity testing may not be needed at this time.

Reproductive Toxicity. No information was located regarding chlorine dioxide- or chlorite-induced reproductive effects in humans. Slightly altered sperm morphology and motility were observed in rats administered sodium chlorite in the drinking water, but treatment did not result in significant alterations in fertility rates or reproductive tissues (Carlton and Smith 1985; Carlton et al. 1987). Repeated oral exposure of male rats to chlorine dioxide or chlorite resulted in significantly decreased testicular DNA synthesis, however (Abdel-Rahman et al. 1984b; Suh et al. 1983). No significant treatment-related effects on fertility rates or sperm parameters were seen in other rats following repeated oral exposure to chlorine dioxide (Carlton et al. 1991).

Couri et al. (1982b) reported an increase in the number of resorbed and dead fetuses in cesarean-delivered litters of pregnant rats receiving chlorite doses $70 mg/kg/day during gestation. However, this may have been a developmental toxicity effect. Additional reproductive toxicity studies could be designed to further investigate the potential for chlorine dioxide or chlorite to induce reproductive effects.

Developmental Toxicity. Epidemiological reports have focused on human populations exposed to chlorine dioxide-treated drinking water (Kanitz et al. 1996; Tuthill et al. 1982). However, study limitations preclude making definitive conclusions regarding the potential for chlorine dioxide- or chlorite-induced developmental toxicity in humans. Results from rat studies indicate that perinatal exposure to chlorine dioxide or chlorite may result in delayed neurodevelopment, observed as decreases in brain size and exploratory and locomotor activities (Mobley et al. 1990; Orme et al. 1985; Taylor and Pfohl 1985; Toth et al. 1990) or decreased auditory startle response (Gill et al. 2000). In some studies, postnatal changes in serum thyroid hormone levels have also been observed (Carlton and Smith 1985; Carlton et al. 1987; Mobley et al. 1990; Orme et al. 1985). These effects have been observed at maternal doses of approximately 6–14 mg/kg/day. Neither chlorine dioxide nor chlorite appear to induce significant gross soft tissue or skeletal abnormalities (Couri et al. 1982b; Harrington et al. 1995b; Suh et al. 1983). Additional developmental toxicity studies in animals should include a mechanistic approach designed to investigate the basis of the observed neurodevelopmental delays and a possible relationship between thyroid hormone effects and neurodevelopmental delays.

Immunotoxicity. Reports of immunotoxicity are restricted to the findings of treatment-related altered thymus and spleen weights in animals exposed to chlorine dioxide or chlorite (Daniel et al. 1990; Gill et al. 2000; Harrington et al. 1995a). Neither chlorine dioxide nor chlorite appear to be of particular immunotoxicity concern. Additional immunotoxicity studies do not appear to be needed at this time.

Neurotoxicity. With the exception of neurodevelopmental effects, chlorine dioxide and chlorite do not appear to present a significant neurotoxicity concern. Additional studies should focus on neurodevelopmental end points (refer to Section 3.12.2).

Epidemiological and Human Dosimetry Studies. Limited information is available regarding health effects in humans following exposure to chlorine dioxide or chlorite. Respiratory effects were reported among individuals who were accidently exposed to concentrated chlorine dioxide vapors (Elkins 1959; Exner-Freisfeld et al. 1986; Ferris et al. 1967, 1979; Gloemme and Lundgren 1957; Kennedy et al. 1991; Meggs et al. 1996). A single case report was located in which an individual ingested approximately 10 g of sodium chlorite in an apparent suicide attempt (Lin and Lim 1993). In a set of controlled studies, male volunteers consumed chlorine dioxide in aqueous solution and submitted blood samples for analysis (Lubbers et al. 1981, 1984a, 1984b). Two epidemiological studies were designed to investigate the potential for adverse effects in communities that utilized chlorine dioxide as a drinking water disinfectant

(Kanitz et al. 1996; Tuthill et al. 1982). However, these studies had limitations in their designs that affect their interpretability. Well-designed epidemiological studies of populations orally exposed to chlorine dioxide in the drinking water could provide valuable information regarding safe levels.

Biomarkers of Exposure and Effect.

Exposure. No known biomarkers of exposure exist for chlorine dioxide. Being a water-soluble, strong oxidizing agent, chlorine dioxide is not likely to be absorbed as parent compound, but rather quickly reduced to chlorite and ultimately chloride ion. Chlorite levels can be measured in biological tissues and fluids, and may serve as an indication of recent exposure to chlorine dioxide or chlorite. Studies could be designed to quantify chlorite levels in various body tissues and fluids; however, it is not known whether such measurements could be used to quantify exposure levels.

Effect. No known chlorine dioxide- or chlorite-specific biomarkers of effect exist. Additional studies of mechanisms of toxicity might provide information that could aid in the search for biomarkers of effect. A human study of methemoglobinemia among persons (especially children and nursing infants) exposed to higher concentrations of chlorine dioxide and chlorite in the drinking water might be beneficial.

Absorption, Distribution, Metabolism, and Excretion. Information regarding the pharmacokinetics of chlorine dioxide and chlorite is predominantly derived from oral studies in laboratory animals. Chlorite (ClO_2^-) does not persist in the atmosphere either in ionic form or as chlorite salt. The rapid appearance of ^{36}Cl in plasma following oral administration of chlorine dioxide ($^{36}ClO_2$) or chlorite ($^{36}ClO_2^-$) has been shown in laboratory animals (Abdel-Rahman et al. 1980a, 1982, 1984a). Limited animal data indicate the presence of ^{36}Cl in plasma following dermal application of Alcide, an antimicrobial compound containing sodium chlorite and lactic acid which rapidly form chlorine dioxide when mixed together (Scatina et al. 1983). In rats, absorbed ^{36}Cl (from $^{36}ClO_2$ or $^{36}ClO_2^-$ sources) is slowly cleared from the blood and is widely distributed throughout the body (Abdel-Rahman et al. 1980a, 1980b, 1982, 1984a). Chlorine dioxide rapidly dissociates, predominantly into chlorite (which itself is highly reactive) and chloride ion (Cl^-), ultimately the major metabolite of both chlorine dioxide and chlorite in biological systems (Abdel-Rahman et al. 1980b, 1984a). Urine is the primary route of elimination, predominantly in the form of chloride ion (Abdel-Rahman et al. 1980a, 1980b, 1984a). Additional pharmacokinetic studies of chlorine dioxide and chlorite should be designed to examine mechanisms of absorption and metabolic changes that might account for observed neurodevelopmental

effects. Such studies might also elucidate mechanisms underlying alterations in various hematological and thyroid hormone parameters of currently unknown significance.

Comparative Toxicokinetics. No studies were located in which toxicokinetics of chlorine dioxide or chlorite were examined in humans. Chlorine dioxide is used as a drinking water disinfectant and readily forms chlorite (ClO_2^-) in aqueous environments. Therefore, humans would be most likely to encounter chlorine dioxide or chlorite via the oral exposure route. Currently, available toxicokinetic information is restricted to animal studies. Additional studies could be designed to examine toxicokinetics in humans orally exposed to chlorine dioxide or chlorite. Results of human and animal studies could then provide a basis for development of PBPK models for species extrapolation.

Methods for Reducing Toxic Effects. No information was located regarding methods for reducing the toxic effects of chlorine dioxide or chlorite. Increasing urinary output might be an effective method for reducing body burden shortly following exposure. Intravenous administration of methylene blue might reduce chlorine dioxide- or chlorite-induced increases in methemoglobin. Future studies should be designed to evaluate mechanisms of chlorine dioxide- and chlorite-mediated toxicity. Results of such mechanistic studies might elucidate methods to reduce the toxic effects.

Children's Susceptibility. Neurodevelopmental delays and postnatal changes in serum thyroid hormone levels have been observed in animals following exposure of their mothers to chlorine dioxide or chlorite during gestation and/or lactation (Carlton and Smith 1985; Carlton et al. 1987; Gill et al. 2000; Mobley et al. 1990; Orme et al. 1985; Taylor and Pfohl 1985; Toth et al. 1990). It is not known whether age-related differences in toxicokinetic parameters exist for chlorine dioxide or chlorite. Additional studies should be designed to further examine neurodevelopmental toxicity and underlying mechanisms.

A human study of methemoglobinemia among children and nursing infants exposed to higher concentrations of chlorine dioxide and chlorite in the drinking water might provide valuable information regarding age-related susceptibility.

Child health data needs relating to exposure are discussed in 6.8.1 Identification of Data Needs: Exposures of Children.

3.12.3 Ongoing Studies

No ongoing studies pertaining to the toxicity or pharmacokinetics of chlorine dioxide or chlorite were located in a search of the Federal Research in Progress database (FEDRIP 2002).